

# EXHIBIT 5

*Lembke Report*

*Confidential — Subject to Protective Order*

## **EXPERT REPORT, ANNA LEMBKE, M.D.**

**February 7, 2024**

### **RELATING TO**

*Cobb County, v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP

PLAINTIFF TRIAL  
EXHIBIT  
**P-01357**

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**A. Background and Qualifications**

1. I am Professor of Psychiatry and Addiction Medicine, Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. From 2016 to 2021, I also held a Courtesy Appointment in the Stanford University Department of Anesthesiology and Pain Medicine. I began my faculty career at Stanford in 2003.

2. I received my undergraduate degree in Humanities from Yale University in 1989, and my medical degree from Stanford University in 1995, where I also completed a partial residency in Pathology (1997) and a full residency in Psychiatry (2000), as well as a Fellowship in Mood Disorders, Department of Psychiatry and Behavioral Sciences (2002).

3. I have been licensed to practice medicine in the State of California from 1995 to the present. I received the DEA-X waiver to prescribe buprenorphine products in 2013. I am a diplomate of the American Board of Psychiatry and Neurology (2003; recertified, 2013), and a diplomate of the American Board of Preventative Medicine (Addiction Medicine) (2021).

4. From 2001 to the present, I have taught medical students, residents, and fellows at Stanford University School of Medicine on a diversity of topics related to psychiatry, addiction, and pain. For example, from 2004 to the present, I have given annual lectures on addiction medicine within the Practice of Medicine (POM) series for Stanford medical students, including topics such as the neurobiology of addiction, how doctors should intervene when they detect substance use problems, and how to have difficult conversations with patients on the topic of substance use, misuse, overuse, and addiction.

5. I received the Stanford Award for Excellence in Academic Teaching, Department of Psychiatry, in 2014 and again in 2018.

6. In 2013, I founded and became the Training/Program Director for Stanford's Addiction Medicine Fellowship, a post-graduate sub-specialty training year in the treatment of addiction for any medical graduate of a U.S. or Canadian medical school and ACGME-accredited residency. In 2020 I was awarded the ASAM Training Directors Award "for outstanding training in the evaluation, treatment, research and teaching of substance use disorders."

7. In 2013, I instituted a monitoring protocol to be followed by prescribers at the Stanford Outpatient Clinic. This protocol required, among other measures, that prescribers check the California Prescription Drug Monitoring Program (PDMP) database, known as "CURES", and consider red flags indicating a risk of diversion or misuse before prescribing controlled substances to patients of the Clinic.

8. As a full time faculty member at the Stanford University School of Medicine, I regularly treat patients with addiction to opioids and other substances. For the last 15 years, my clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction. As an integral part of my practice, I work with these patients to develop treatment plans that will

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address their pain while making appropriate efforts to reduce (taper) or eliminate use of opioids, and/or treat their opioid addiction. Such plans can include non-opioid medications for pain, as well as alternative, non-pharmaceutical modalities, and counseling, with a dual focus on treating the underlying painful condition and the substance use disorder. I frequently collaborate with pain and primary care colleagues concerning populations with chronic pain and substance use disorders.

9. In 2015, I received the Stanford Chairman's Award for Clinical Innovation for developing inpatient and outpatient clinical services dedicated to helping people with substance use problems.

10. In January 2015, I was appointed by Governor Jerry Brown to the Research Advisory Panel of California. I served on the Panel until 2017. I, along with the other Panel members, was tasked with assessing the safety of clinical trials to be conducted in the state of California using controlled substances, such as opioids. In this capacity, I applied my knowledge and experience to the review of study designs and protocols, and I made recommendations for procedures to protect patients in these trials, including, in particular, protection from potential harmful effects of opioids.

11. From 2015 to 2019, I served on the Board of the California Society of Addiction Medicine (CSAM). I have been a member of CSAM, and the American Society of Addiction Medicine (ASAM), since 2011.

12. In 2015-2016 I chaired the Planning Committee for the CSAM Annual Addiction Medicine Conference.

13. In 2016, I became president of the Addiction Medicine Fellowship Directors Association (AMFDA).

14. In 2016, I led a program funded by the Stanford Center for Continuing Medical Education (SCCME), titled, "Tapering Patients Off of Chronic Opioid Therapy."<sup>1</sup>

15. Since 2016, I have chaired the Addiction Medicine Task Force, Stanford University School of Medicine. The goal of the Task Force is to re-evaluate and re-create the medical school curriculum on addiction and safe prescribing of addictive substances. I have served as MedScholar Advisor on the topic of *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine. The new medical school curriculum we have created includes didactics on the neurobiology of addiction, the treatment of addiction, the management of opioid prescribing in the setting of chronic pain,<sup>2</sup> and the history and origins of the opioid epidemic.

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<sup>1</sup> *How to Taper Patients Off of Chronic Opioid Therapy*, Stanford University School of Medicine, <https://med.stanford.edu/cme/courses/online/opioid-taper.html>.

<sup>2</sup> Chronic pain is frequently considered to be pain that lasts longer than 3 months. See e.g., Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645, at p. 1625.

16. In 2019, the Stanford Center for Health Education asked me to lead and design an online course on addiction for Stanford learners all over the world. This course is called “The Psychology of Addiction and Recovery” and explores concepts of addiction through time, risk factors for addiction, and treatments for addiction including biological, psychological, and public policy approaches. The course has been available since August 2020.

17. I am the author of a book on the prescription drug epidemic: *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* (Johns Hopkins University Press, 2016).<sup>3</sup> My book was highlighted in the *New York Times* as one of the top five books to read to understand the opioid epidemic.<sup>4</sup>

18. I have published over 100 peer-reviewed articles, chapters, and commentaries, which have appeared in the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Pain Medicine*, *Journal of General Internal Medicine*, *Addiction*, and other peer reviewed journals. Many of these publications address the diagnosis and treatment of addiction, as well as the treatment of pain. I have also published articles on the importance of teaching addiction medicine in medical school, residency, and fellowship.

19. In 2016, I co-authored a peer-reviewed article, “Weighing the Risks and Benefits of Chronic Opioid Therapy,” which addressed issues of opioid misuse and addiction, risk assessment and mitigation, patient education, tapering to reduce or end opioid exposure, tolerance, dependence, and risks of overdose.<sup>5</sup> *American Family Physician* is among the most read family physician peer reviewed journals. The readership includes 32,000 medical students and over 3,700 nurse practitioner and physician assistant subscribers.

20. Also in 2016, I published an article entitled, “Be Sure to Check the PDMP before Prescribing Controlled Medications.”<sup>6</sup> This article discussed the importance of reviewing the Prescription Drug Monitoring Database to identify “red flags” indicating the potential for diversion and misuse, including drug combinations of opioids and benzodiazepines, with or without additional “cocktail drugs,” as well as multiple prescriptions for the same or similar drug from multiple doctors (“doctor shopping”). I refer to the California CURES/PDMP on a regular basis, to investigate and resolve red flags among my own patients, and this database is similar to those that pharmacies could and should have relied upon for the same purposes in other states, as detailed in this Report.

21. In 2016, I co-authored a Research Letter in *JAMA Internal Medicine* that examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is “a widespread practice relatively indifferent to individual physicians, specialty or

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<sup>3</sup> Lembke, Anna. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why Its so Hard to Stop*. Johns Hopkins University Press, 2016.

<sup>4</sup> Abigail Zuger, A Doctor's Guide to What to Read on the Opioid Crisis, *N.Y. Times* (Dec. 17, 2018)

<sup>5</sup> Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician*. 2016; 93(12):982-990.

<sup>6</sup> Lembke A. Be sure to check the PDMP before prescribing controlled medications. *Psychiatric News* (June 17, 2016).



region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective.”<sup>7</sup> This article has been cited 166 times in the 8 years since its publication,<sup>8</sup> and demonstrates that the epidemic of opioid drug misuse and addiction is attributable to many prescribers, including but not limited to high-frequency prescribers, who are sometimes referred to as “pill mills.”

22. In 2016, I co-authored a Research Letter in *JAMA Psychiatry* on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment and access to that treatment.<sup>9</sup>

23. In 2018, I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.<sup>10,11</sup>

24. Also in 2018, I co-authored a Perspective in the *New England Journal of Medicine*, entitled, “Our Other Prescription Drug Problem,” which addressed the risks of benzodiazepines, such as Xanax (alprazolam), and the FDA’s 2016 addition of a black box warning of the dangers of co-prescribing benzodiazepines with opioids due to increased risk of respiratory suppression and death.<sup>12</sup> In this article, I reiterated the importance of reviewing the PDMP to reduce inappropriate use of controlled substances, the overdoses and deaths that result from such uses, and the co-prescribing of drugs in these classes as a “red flag” requiring diligent investigation.

25. In 2019, I co-authored two articles in peer-reviewed journals on how to transition hospitalized patients with opioid use disorder onto opioid agonist therapy while still managing their pain conditions.<sup>13</sup> Opioid agonist therapy refers here to buprenorphine, an opioid used to

<sup>7</sup> Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med.* December 2015;1-3. <http://dx.doi.org/10.1001/jamainternmed.2015.6662>, at pp. 260-261.

<sup>8</sup> “Distribution of opioids by different types of medicare prescribers” Google Scholar Results [https://scholar.google.com/scholar?hl=en&as\\_sdt=0%2C5&q=Lembke+Distribution+of+opioids+by+different+type+s+of+medicare+prescribers&btnG=](https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Lembke+Distribution+of+opioids+by+different+type+s+of+medicare+prescribers&btnG=) (last accessed January 8, 2024)

<sup>9</sup> Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry.* 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390.

<sup>10</sup> Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin.* 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002.

<sup>11</sup> Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med.* 2018;(February):1-4. doi:10.1093/pm/pny019.

<sup>12</sup> Lembke A, Papac J, Humphreys K. Our other prescription drug problem. *N Engl J Med.* 2018;378(8):693-695. This article, published in 2018, was written and submitted for review in 2017, before I was retained as an expert witness in opioid litigation.

<sup>13</sup> Raheemullah, A., Lembke, A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment, *JAMA Internal Medicine*, 2019; 179(3):427-428. Raheemullah, A., Lembke, A. Buprenorphine Induction Without Opioid Withdrawal: A Case Series of 15 Opioid-Dependent Inpatients Induced on Buprenorphine Using Microdoses of Transdermal Buprenorphine. *American Journal of Therapeutics*, 2019; 0:1-7.

treat severe opioid use disorder, but which can be difficult to initiate in patients already on opioids due to its unique chemical properties (high binding affinity). The report by Bodnar *et al.* builds upon this work, showing that intravenous buprenorphine microinduction can be an effective way to transition hospitalized patients on full agonist opioids to buprenorphine.<sup>14</sup>

26. In 2020, I co-authored a second peer-reviewed article on the risks of opioid and benzodiazepine co-prescribing.<sup>15</sup>

27. In 2020, I was selected to serve as a member of the Stanford-*Lancet* Commission on the North American Opioid Crisis, which brought together 18 experts from around the US and Canada on various aspects of the opioid crisis in order to develop and draft a coherent, empirically-grounded analysis of the causes and solutions to the opioid crisis.<sup>16</sup> I participated in the preparation of the peer-reviewed Commission Report, published in February 2022.<sup>17</sup> The Commission Report specifically identifies and describes the role of the marketing and promotional conduct of the entities that comprise the chain of prescription opioid distribution, including manufacturers, distributors, and pharmacies, as a cause of the opioid epidemic. The Commission Report cites my 2016 book, *Drug Dealer, MD: How Doctor Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, among its references. The findings and recommendations of the published Report, discussed below at §C.4, §C.6, §C.12, §C.14 and §C.15, were the result of a consensus that required approval by at least 90 percent of Commission members. Since its publication, the Stanford-*Lancet* Commission Report has been widely cited.<sup>18</sup>

28. I have devoted a significant portion of my professional career to the development of a patient-centered protocol to reduce or discontinue prescription opioid use among individuals with opioid dependence and chronic pain, called the BRAVO Protocol. This academic detailing material, free of commercial bias, includes but is not limited to infographic handouts, a website platform (<https://www.oregonpainguidance.org/guideline/tapering/>), and a free Stanford-

<sup>14</sup> Bodnar A, *et al.* Use of intravenous buprenorphine microdosing to initiate medication for opioid use disorder in a patient with co-occurring pain: Case report. *Journal of Addictive Diseases*. 2023;1-6, at p. 3. Bodner *et al.* cite to a 2018 article, which I co-authored, discussed above at ¶23.

<sup>15</sup> Azad, Lembke, A. *et al.* Patterns of Opioid and Benzodiazepine Use in Opioid-Naïve Patients with Newly Diagnosed Low Back and Lower Extremity Pain. *J Gen Intern Med*, 2019, 35(1):291-297. doi: 10.1007/s11606-019-05549-8.

<sup>16</sup> My fellow Commissioners included distinguished clinicians, researchers, educators, and public policymakers, with wide-ranging expertise from addiction, biochemistry, emergency medicine, epidemiology, health economics, internal medicine, law, pain medicine, public policy, psychiatry, pharmacology, and public health.

<sup>17</sup> Humphreys K, *et al.* Responding to the opioid crisis in North America and beyond: Recommendations of the Stanford-*Lancet* Commission. The *Lancet* Commissions. (Feb. 2, 2022), [https://doi.org/10.1016/S0140-6736\(21\)02252-2](https://doi.org/10.1016/S0140-6736(21)02252-2). (“Stanford-*Lancet* Commission”)

<sup>18</sup> See, e.g., Dennett, J. M., & Gonsalves, G. S. (2023). Early OxyContin Marketing Linked To Long-Term Spread Of Infectious Diseases Associated With Injection Drug Use. *Health Affairs (Project Hope)*, 101377hlthaff202300146. Advance online publication: “[P]olicy makers should take action to proactively prevent future public health crises. This could be accomplished by implementing specific recommendations of the Stanford-*Lancet* Commission on the North American Opioid Crisis to limit the influence of the pharmaceutical industry on both opioid prescribers and regulators.”

supported, online, continuing medical education course (<https://med.stanford.edu/cme/courses/online/opioid-taper.html>), enduring web-based material (<https://www.oregonpainguidance.org/guideline/tapering/>), and peer-reviewed publications. The BRAVO Protocol has been widely disseminated and recognized by leading authorities. In 2019, the United States Department of Health and Human Services (HHS) was preparing to issue the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. Authors of the HHS Guidelines asked for permission to include a decision-making “flow chart” from the BRAVO Protocol and a previously published article that I co-authored in the *Annals of Internal Medicine* in August 2019. That permission was granted, and the HHS Guidelines included an adaptation of our published decision tree, providing recommendations on how and when to taper patients from long-term opioid use.<sup>19</sup> On October 10, 2019, the *Journal of the American Medical Association (JAMA)* published a commentary about the HHS Guidelines, authored by officials of the United States Centers for Disease Control and the National Institute on Drug Abuse.<sup>20</sup> In addition, in January 2020, *American Family Physician* published my article, “Tapering Long-Term Opioid Therapy,” which was offered to professionals for 6 hours of Continuing Medical Education (CME) credit, further documenting the acceptance of my work in this area.<sup>21</sup> The BRAVO Protocol material and accompanying free Stanford CME course have been adopted in several states as part of CME on safe opioid prescribing. The BRAVO Protocol has been used as a guiding framework for opioid tapering in clinics across the country (see Appendix V).<sup>22</sup>

29. I have testified before the United States House of Representatives on the opioid epidemic and ways to mitigate harms caused by that epidemic, and I have presented at numerous conferences before governmental, professional, academic, and lay audiences on related topics. In January 2022, I gave a presentation to Kentucky circuit court judges on the role of the opioid industry in promoting misleading messages about opioids. This presentation was given at the invitation of the “Science and the Law” initiative at the American Association for the Advancement of Science (AAAS), the largest multidisciplinary scientific society in the world, and a 501(c)(3) non-governmental organization, in conjunction with the Administrative Office of Kentucky Courts. The invitation stated, “Given your expertise, AAAS would like to invite you to provide an approximately 25 minute presentation on the background (e.g., origins, sociology, current status) of the opioid crisis.” My PowerPoint presentation included slides outlining the

<sup>19</sup> Chou, *et al.*, Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med.* 2019; 171(6):427-429. As discussed in this Report, it is essential to patients’ well-being that proper, patient-centered methods of tapering are followed, to reduce or eliminate opioid use without imposing unnecessary risks associated with rapid or formulaic discontinuation of these drugs.

<sup>20</sup> Dowell, *et al.*, Patient-Centered Reduction or Discontinuation of Long-Term Opioid Analgesics. *JAMA.* 2019;322(19):1855-1856. doi:10.1001/jama.2019.16409; Chou, *et al.*, Rethinking Opioid Dose Tapering, Prescription Opioid Dependence, and Indications for Buprenorphine, *Ann Intern Med.* 2019;171(6):427-429. doi: 10.7326/M19-1488.; United States Department of Health and Human Services. HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics. (October 2019); [https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage\\_Reduction\\_Discontinuation.pdf](https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf), at p. 3.

<sup>21</sup> Lembke A., Tapering Long-Term Opioid Therapy. *Am Fam Physician* 2020; 101(1):49-52.

<sup>22</sup> See also Perez, M. “Tapering Long-Term Opioids Can Be Both Patient-Centered and Evidence-Based.” Washington Medical Commission, (2021). <https://wmc.wa.gov/sites/default/files/public/Newsletter/opioids.pdf>, for example of successful use of BRAVO protocol.

myths promoted by the Pharmaceutical Opioid Industry<sup>23</sup> and summarizing the evidence contradicting those myths. The misleading messages, including overstated efficacy for chronic pain and understatement of the risk of addiction, are identical to those stated in my Report, below. In February 2022, I gave a similar presentation to elected representatives in Edmonton, Canada at the invitation of the Ministerial Assistant to the Associate-Minister of Mental Health and Addictions. In January 2023 I joined the Recovery Expert Advisory Panel (REAP) at the invitation of the Alberta Ministry of Mental Health and Addiction, Calgary, Canada.

30. Since the publication of my book, *Drug Dealer, MD*, I have been invited to make presentations to doctors and the public, regarding the causes of the opioid epidemic and how we can combat it. A significant portion of my work in this area consists of describing the false and misleading messages promoted by the Pharmaceutical Opioid Industry as detailed in this Report, including but not limited to unsupported claims of long-term efficacy for chronic pain, false representations of the risk of addiction, downplaying the risks of dependence and withdrawal, and misinforming doctors about the extent to which opioid doses could safely be increased. As to all of these subjects, it has been my experience that audiences of professionals and lay persons alike continue to be misled by the decades-long campaign of misinformation promoted through the Industry's marketing of opioids. "Academic detailing" is the process of providing accurate information to medical providers about the risks and benefits of a drug, to balance and re-educate after exposure to one-sided and inaccurate messaging from the detailers who have conveyed Industry messages to those providers over extended periods of time. As noted by the Report of the Association of Schools and Programs of Public Health (ASPPH), issued in November 2019, there is a need for "*extensive academic detailing and counter-detailing on opioids* to correct the inaccurate and misleading claims previously made by the companies that manufacture those drugs, messages that continue to confuse or mislead some patients and prescribers."<sup>24</sup> I began and performed my work in academic detailing before any connection or thought of involvement in litigation, and I continue in this role to counter the false and misleading marketing messages of the Pharmaceutical Opioid Industry.

31. I have substantial experience in the study and teaching on the marketing of opioids, the impacts of such marketing on prescribing habits of physicians, and the effects of market-driven prescribing as a cause of the ongoing opioid epidemic. I have taught extensively at Stanford University and other institutions of higher learning on the ways in which the Pharmaceutical Opioid Industry marketed prescription opioids as both more effective and less addictive than they really are. My lectures have included coverage of overt, aggressive marketing tactics (such as detailing by company sales representatives, coupons for free or discounted opioids, and free lunches or dinners provided to doctors), as well as the Industry's covert partnerships with, and financial support for, organizations with significant influence on the

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<sup>23</sup> The term Pharmaceutical Opioid Industry includes the Defendants in this case, including Publix Super Markets, Inc. (Publix) and The Kroger Co. and Kroger corporate entities. The use of this term is an expression of my opinion that responsibility for the opioid epidemic is shared among all levels of the supply chain, including manufacturers, distributors, and pharmacies. Specific examples of the conduct of particular members of the Industry, including Publix and Kroger, are provided throughout this Report; responsibility of entities other than the Pharmaceutical Opioid Industry is also discussed, at §C.14, below.

<sup>24</sup> Association of Schools & Programs of Public Health (ASPPH) Report, "Bringing Science to Bear on Opioids," 11/01/2019, [https://aspph-wp-production.s3.us-east-1.amazonaws.com/wp-content/uploads/2019/09/ASPPH.Opioids.FINAL\\_11.01.20191.pdf](https://aspph-wp-production.s3.us-east-1.amazonaws.com/wp-content/uploads/2019/09/ASPPH.Opioids.FINAL_11.01.20191.pdf), at p. 21.

practice of medicine (*e.g.*, The Joint Commission on Accreditation of Healthcare Organizations (JCAHO, The Joint Commission, or TJC), The Federation of State Medical Boards (FSMB), and professional medical societies such as the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS)). My lectures have also included discussion of my firsthand experience of these marketing tactics, as well as their continuing impact on several generations of doctors. I have lectured on the Industry's extensive publications in the peer-reviewed medical literature, explaining that these tactics influence physicians' opioid prescribing practices. I am frequently asked to peer-review articles for publication in medical journals regarding the influence of the pharmaceutical industry's marketing on prescribing practices. I have given lectures on these subjects to Stanford undergraduates, Stanford business, law, public health, and medical students, among others. I have also spoken on these topics widely outside of Stanford. In the fall of 2020, I taught at Duke University's Global Health Institute on the subject of "market driven epidemics," including the opioid epidemic.

32. Since the time of my earlier reports in this litigation, I have conducted further research concerning the role of pharmacies in the opioid epidemic, and I have also reviewed documents provided by counsel on that subject. These documents and their significance are discussed in Opinion 6, below.

33. Throughout my career I have interacted with pharmacies and pharmacists thousands of times. On any given clinic day I will have interactions with multiple pharmacies and pharmacists pertaining to prescriptions I have written or others have written for patients in my care. The nature of these interactions with pharmacists can be accurately described as a partnership between professionals, with the overarching goal being the safety and the best interests of our patients. Due to my role as a frequent prescriber of scheduled pharmaceuticals, I am familiar with the federal Controlled Substances Act (CSA), which includes obligations to prevent unauthorized or illegitimate prescriptions of these potentially dangerous drugs, and to identify and investigate "red flags" which refers to any signs or indications that a particular prescription may be outside of the boundaries of a legitimate medical purpose. I am also aware that "The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription."<sup>25</sup>

34. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as "pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. ..." I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.<sup>26,27</sup> As a regular and ongoing part of my practice, I conduct

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<sup>25</sup> 21 C.F.R. §1306.04(a). [I think it is stronger to just cite the regulation]

<sup>26</sup> *Chen et. al*, "Distribution of Opioids," fn. 7, above, at p. 259.

<sup>27</sup> *Lembke, et al.*, "Use of Opioid Agonist Therapy," fn. 9, above, at p. 990.



*Lembke Report*

*Confidential — Subject to Protective Order*

literature searches of research on the subjects of addiction and pain treatment, which is essential to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed in Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

35. Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.

36. Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

37. Attached as Exhibit C is a statement of my compensation for services performed in this case.

38. Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

## **B. Opinions**

For the reasons set forth in detail in this Report, I hold the following opinions:

**1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.**

**2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.**

**3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.**

**4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through an aggressive sales force, key opinion leaders, medical school curricula, continuing medical education courses, clinical decision support tools, professional**

**medical societies, patient advocacy groups, the Federation of State Medical Boards, and The Joint Commission.**

**5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids, coupons to discount opioids, and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.**

**6. Pharmacies leveraged their unique and pivotal position in the opioid supply chain to contribute to the unprecedented and unchecked flow of opioid pain pills into the community. They alone had direct contact with opioid manufacturers and distributors upstream, and patients and prescribers downstream. Their coordinated efforts included direct mailings and media campaigns, continuing medical education courses for pharmacists, partnering with pro-opioid industry advocacy and lobbying organization, and creating stores where prescription opioids were readily available and abundant, sometimes called “Super Stores.” They ignored ‘red flags’ for misuse and diversion (including concerns expressed by their own pharmacists), and failed to provide pharmacists with sufficient time, resources, or incentives to investigate red flags. They also failed to use or analyze their own dispensing data to assist pharmacies in identifying red flags. By increasing and assuring the supply of opioids, and failing to provide effective controls against diversion, pharmacies contributed to opioid misuse, addiction, dependence, and death.**

**7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.**

**8. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is “rare,” or “less than 1%,” when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.**

**9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).**

**10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).**

**11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).**

**12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an**

**outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990s and continuing to the present day.**

**13. There is no doubt a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.**

**14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.**

**15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.**

### **C. Detailed Statement of Opinions**

**1. The addictive nature of medicinal opioids has been known for centuries. The Pharmaceutical Opioid Industry's misrepresentations of the safety and efficacy of prescription opioids reversed a century of appropriate restrictions on the use of these dangerous drugs, and substantially contributed to the current opioid epidemic.**

- a. Opioids are among the world's oldest known drugs. Use of opium from the poppy plant for medical, recreational, and religious purposes can be traced throughout history and across continents, beginning in the 4<sup>th</sup> century B.C.<sup>28</sup>
- b. In the 19th century, two major scientific advances in medicinal opioids had far-reaching consequences. In 1804, German pharmacist Friedrich Serturner isolated morphine, an opioid alkaloid derived from opium and ten times as potent.<sup>29</sup> In 1855, Alexander Wood invented the hypodermic syringe, making possible fast easy administration of morphine.<sup>30</sup>

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<sup>28</sup> Lembke A. Psychology of Addiction and Recovery. Lecture: History of Addiction (Stanford University, Fall/Winter 2020)

<sup>29</sup> Meldrum ML. A capsule history of pain management. *JAMA*. 2003;290:2470-2475, at p. 2471

<sup>30</sup> Lembke, "Drug Dealer, MD", fn 3, above, at p. 42. *See also* Meldrum, "Capsule history", fn. 29, above, at p. 2471.



- c. It was assumed (wrongly) that opioids administered by a doctor using a hypodermic syringe would not be addictive. During the Civil War, opium, laudanum, and hypodermic morphine were used extensively to treat soldiers and Victorian housewives alike. Hypodermic morphine soon became the major driver of American's first opioid epidemic. Hundreds of reports in late nineteenth century medical journals detailed iatrogenic (physician-initiated) cases of morphine addiction. The risk of addiction increased in cases where doctors continued to administer hypodermic morphine over long periods of time for protracted illnesses.<sup>31</sup> The two most important risk factors were exposure to opioids and a history of chronic illness. In the 1870s and 1880s, America's per capita consumption of opioids tripled.<sup>32</sup>
- d. In 1897, Bayer chemists, trying to find a less addictive form of morphine, synthesized heroin. Heroin was marketed by Bayer as a cough and cold remedy alongside Bayer Aspirin from 1898 to 1910.<sup>33</sup>
- e. The opioid addiction epidemic of the late 19<sup>th</sup> and early 20<sup>th</sup> century (Narcomania) led to ever-stricter laws and regulations regarding the prescribing and dispensing of opioids in medical practice, beginning in the early 1900s with the Harrison Narcotic Act, which effectively made heroin illegal.<sup>34</sup>
- f. As a result, the first several decades of the 1900s saw a steady decrease in the per capita consumption of medicinal opioids.<sup>35</sup>
- g. Subsequent opioid epidemics in the 1940s and 1970s were smaller scale heroin epidemics unrelated to medical prescribing.<sup>36</sup> They were targeted and quelled through a process of repatriating Vietnam War veterans, criminalization, and methadone maintenance treatment.<sup>37</sup>
- h. In 1970 the Controlled Substances Act (CSA) was passed, which serves as the cornerstone of today's drug scheduling system.<sup>38</sup> Schedule I drugs were prohibited. Schedule II drugs, including medicinal opioids, were tightly regulated with dire warnings of addictive potential, no prescription refills, triplicate order forms for transfers, production quotas, enhanced storage

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<sup>31</sup> Courtwright DT. "Dark Paradise: A History of Opiate Addiction in America". Harvard University Press; 2001, at pp. 46-47.

<sup>32</sup> *Id.* at pp. 2-3 and 62-63.

<sup>33</sup> Lembke, "Drug Dealer, MD", fn. 3, above, at pp. 30-31

<sup>34</sup> *Id.* at footnote p. 57.

<sup>35</sup> Courtwright, "Dark Paradise", fn. 31, above, at p. 29

<sup>36</sup> *Id.* at p. 8.

<sup>37</sup> *Id.* at p. xii.

<sup>38</sup> Lembke, "Drug, Dealer MD", fn. 3, above, at pp. 57, 31 and 5.

security requirements, and preapproval for all imports and exports.<sup>39</sup> Drugs included in Schedules III-V were considered to have lower potential for abuse.

- i. Medical training and education throughout the 20th century, save for the last two-plus decades, was filled with warnings about the addictive potential of medicinal opioids, even when prescribed to patients with severe pain and dire illness, but especially when used long term in the treatment of chronic pain. Physicians were urged to use opioids sparingly, for short duration, and only in cases of severe trauma and at the end of life.<sup>40</sup> For example, a peer-reviewed study published in 1954 concluded “Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.”<sup>41</sup>
- j. The current opioid epidemic in the United States, occurring almost exactly 100 years after the first major opioid epidemic, was ushered in by the reversal of a century of prudential legislation and medical training. The result, since the 1990s, has been a prolonged period of opioid overprescribing with concomitant opioid addiction, dependence, and overdose death. When Defendants claim that knowledge of the addictive potential of medicinal opioids is new, they ignore 100 years of medical experience, knowledge, and legislation.<sup>42</sup> The addictive nature of medicinal opioids has been known for centuries.

**2. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an addictive drug is increased, more people become addicted to and suffer the harms of that drug. Prescription opioids are as addictive as heroin, and the Defendants’ conduct in promoting increased supply and widespread access to prescription opioids has resulted in an epidemic of opioid addiction and overdose death.**

- a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) uses the term “substance use disorder” to denote

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<sup>39</sup> *Id.* at p. 5.

<sup>40</sup> *Id.* at pp. 56-57.

<sup>41</sup> Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc.* 1954;156(7):684-691, at p. 690.

<sup>42</sup> Lembke, “Drug Dealer, MD”, fn. 3, above, at pp. 56-57.

addiction. I use the terms “opioid addiction” and “opioid use disorder” interchangeably here.

- b. DSM-5 denotes 11 different criteria to diagnose opioid use disorder (OUD).<sup>43</sup> A short-hand way to remember these criteria is the “four C’s”: Control, Compulsion, Craving, and continued use despite Consequences.
  - i. Control refers to out-of-control use, for example using more than intended, or an inability to cut back use when necessary.
  - ii. Compulsion refers to mental preoccupation with using against a conscious desire to abstain.
  - iii. Craving refers to physiologic and/or mental states of wanting.
  - iv. Consequences refers to the social, legal, economic, interpersonal, and other problems that arise as a result of use, yet which still do not deter use.
- c. The physiological phenomena of tolerance and withdrawal are included in the DSM-5 criteria, but they are not required in order to make the diagnosis of opioid use disorder/addiction. In other words, tolerance and withdrawal are recognized as separate physiologic phenomena often seen in addiction, but not definitional for addiction. Further, under DSM-5, the criteria of tolerance and withdrawal do not count toward a diagnosis of addiction when a patient is prescribed opioids under the supervision of a doctor, making it more difficult to diagnose addiction to prescription opioids. As discussed later in this Report, Defendants influenced this definition by characterizing dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.
- d. The DSM-5 also recognizes that addiction is a spectrum disorder, divided into mild, moderate, and severe, based on the number of criteria met.<sup>44</sup>
- e. ASAM has defined addiction as follows: “Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual’s life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic

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<sup>43</sup> *Diagnostic and Statistical Manual of Mental Disorders*. (DSM-5) Washington, DC: American Psychiatric Association; 2013 at p. 541.

<sup>44</sup> *Id.* at pp. 541-542.

diseases”<sup>45</sup> This ASAM definition of addiction is consistent with but not identical to that of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The ASAM definition does not single out any specific substance, highlighting the idea that all addictive drugs work on the same common brain pathway.

- f. From a neuroscience perspective, addiction is a disorder of the brain’s reward circuitry.<sup>46</sup>
  - i. Opioids, in addition to binding the *mu*-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.
  - ii. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.<sup>47</sup> By hijacking the brain’s reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice. The cycle of neuroadaptation is illustrated below<sup>48</sup>:

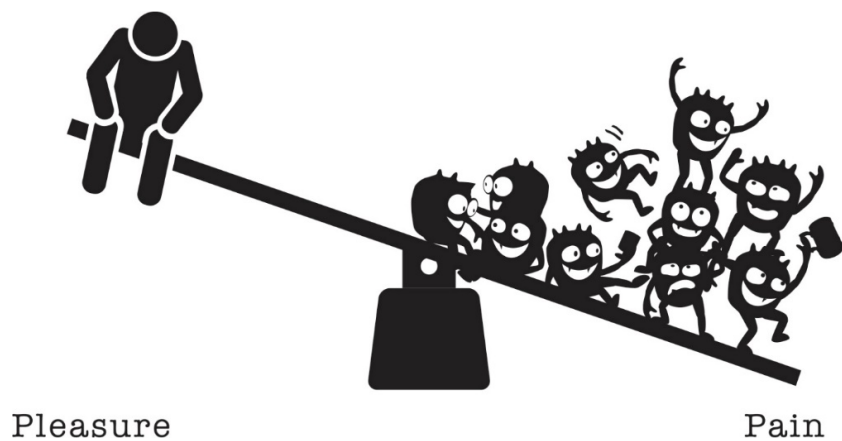
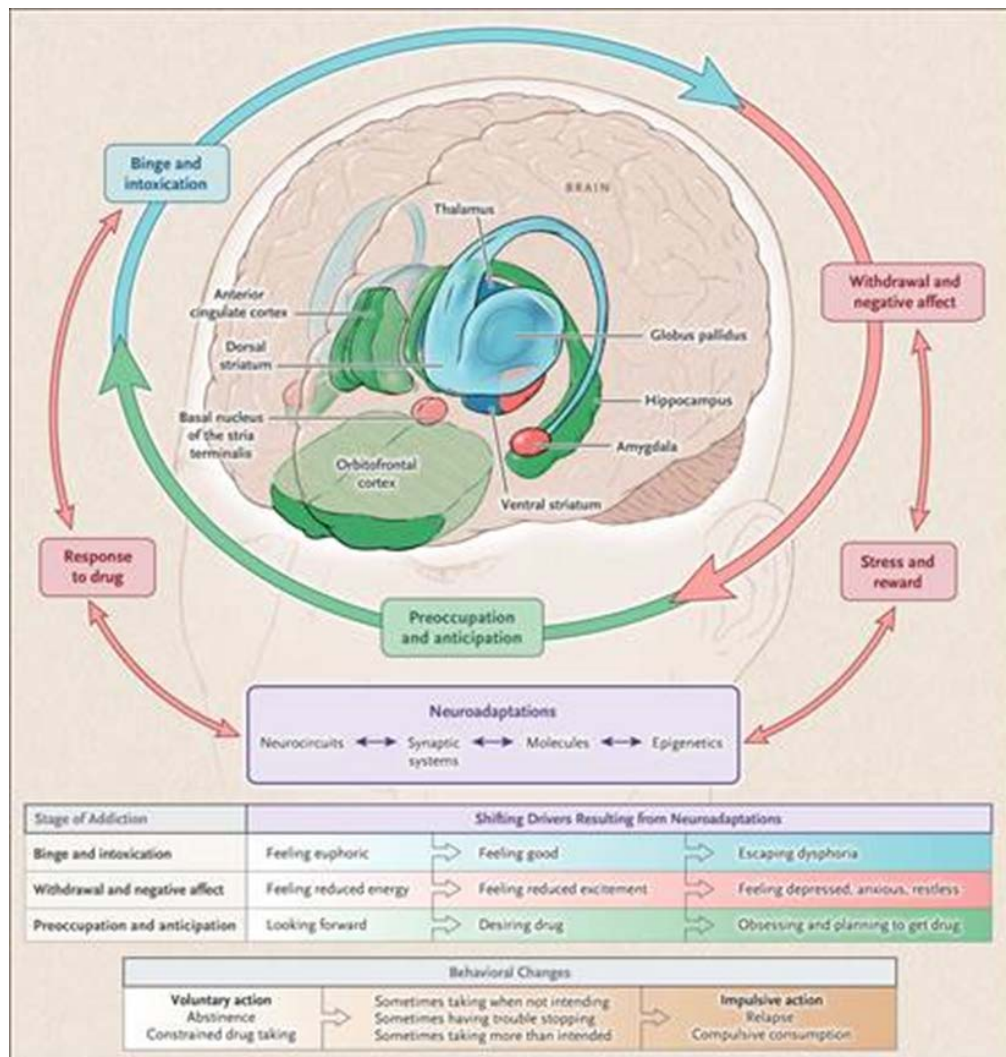
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<sup>45</sup> American Society of Addiction Medicine (ASAM) Definition of Addiction. [https://www.asam.org/docs/default-source/quality-science/asam's-2019-definition-of-addiction-\(1\).pdf?sfvrsn=b8b64fc2\\_2](https://www.asam.org/docs/default-source/quality-science/asam's-2019-definition-of-addiction-(1).pdf?sfvrsn=b8b64fc2_2), (adopted September 15, 2019), at p. 2. Prior to 2019, ASAM defined addiction as follows: “Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.” <https://www.asam.org/resources/definition-of-addiction>, at p. 1. (last accessed June 20, 2018)

<sup>46</sup> Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4.

<sup>47</sup> Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014.

<sup>48</sup> Volkow, ND., *et al.*, Neurobiologic Advances from the Brain Disease Model of Addiction. *N Engl J Med*. 2016; 374:363-371, Figure 1.

**Cycle of Neuroadaptation<sup>49</sup>**<sup>49</sup> *Id.*



- g. The image above is intended as a representation of the effect of opioids on the neurocircuitry of the brain. Its use has been permitted as a demonstrative accompaniment to my testimony before juries in the MDL and New York State courts in October and July, 2021, respectively. As I have explained in that testimony, dopamine is a neurotransmitter produced in the normal human brain and is essential for the experience of pleasure, motivation, and reward. Pleasure and pain are co-located in the brain and work like opposite sides of a balance. One of the overarching rules governing that balance is that it wants to remain level. Opioids, whether in prescription or illicit forms, disrupt the balance by inducing an abnormally large influx of dopamine. This results in an initial feeling of intense pleasure, followed by pain in the form of withdrawal. This is represented by the “gremlins” on the right side of the image. The addicted individual then seeks another dose of the opioid, not to feel well, but rather to restore a level balance and combat the pain and other negative sensations that accompany withdrawal.
- h. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction.
  - i. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review “Opioid Abuse in Chronic Pain” in the *New England Journal of Medicine* (2016), “no patient is immune to addiction.”<sup>50</sup> Similarly, as stated by the CDC, “Anyone who takes prescription opioids can become addicted to them.”<sup>51</sup> The authors conclude, and I agree, “The most important risk factor for opioid analgesic-associated dependence or overdose is not a feature of any individual patient but simply involves receiving a prescription for opioids.”<sup>52</sup>
  - ii. Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed, as illustrated below.<sup>53</sup> The first image is taken from actual MRIs of control and exposed subjects, published in a scientific journal; the second

<sup>50</sup> Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMr1507771, at p. 1254.

<sup>51</sup> Centers for Disease Control and Prevention. *Prescription Opioids*.

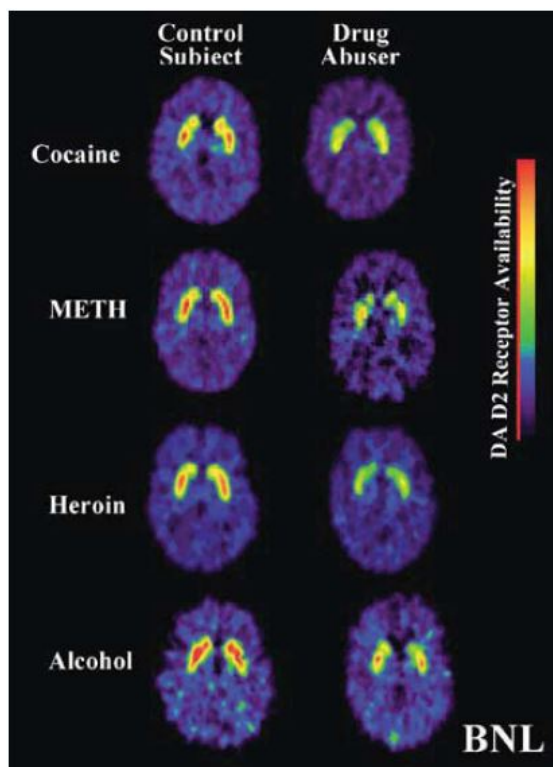
<https://www.cdc.gov/drugoverdose/opioids/prescribed.html> (last updated August 29, 2017)

<sup>52</sup> Dowell D, Kunins HV, Farley, TA. Opioid analgesia – Risky drugs, not risky patients. *JAMA*. 2013;309(21):2219-2220, at p. 2219.

<sup>53</sup> Koob *et.al*, “Neurocircuitry,” fn.46, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557.

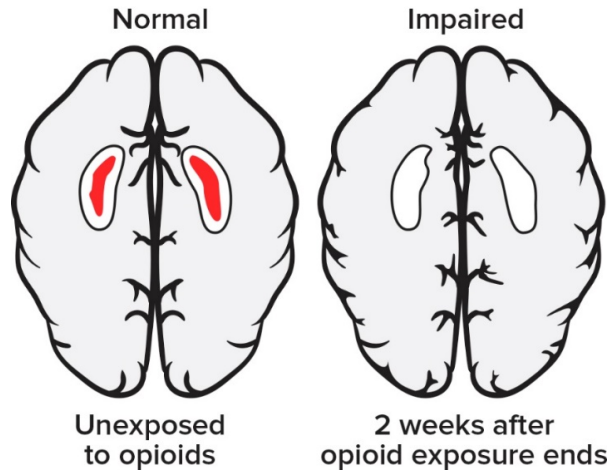
image is a simplified version that is intended to make the dopamine deficit state more comprehensible, where red indicates normal dopamine activity and lack of red indicates abnormal dopamine activity.

### The Effect of Addiction on Dopamine Receptors<sup>54</sup>



<sup>54</sup> Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Molecular Psychiatry*. 2004;9:557-569, at p. 562.

## DOPAMINE ACTIVITY



- i. Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance.
- j. The current opioid epidemic is a tragic and compelling example of increased access leading to increased addiction and related death. The quadrupling of opioid prescribing between 1999 and 2012, combined with widespread distribution of those opioids to every corner of America, does not merely correlate with rising rates of opioid addiction and related deaths, it is causative.
  - i. A Task Force appointed by the Association of Schools and Programs in Public Health (ASPPH), issued a Report on November 1, 2019, concluding, “The *tremendous expansion of the supply* of powerful (high-potency as well as long-acting) prescription opioids led to scaled increases in prescription opioid dependence, and the transition of many to illicit opioids, including fentanyl and its analogs, which have subsequently driven exponential increases in overdose.”<sup>55</sup> The report also stated that addiction, or Opioid Use Disorder, “is caused by repeated exposure to opioids.”<sup>56</sup> ASPPH consists of over 120 member institutions accredited by the Council on Education for Public Health, including programs throughout the United States.<sup>57</sup> The Task Force was appointed by the ASPPH board of directors, and was composed of 14 “recognized experts in the field.” I agree with these statements of the ASPPH Task Force, which are consistent with, and supportive of, the opinions I have expressed in this Report, and in my work prior to becoming involved in litigation related to the opioid epidemic.

<sup>55</sup> ASPPH Report, “Bringing Science to Bear on Opioids,” fn.24, above, at p. 8 (emphasis added).

<sup>56</sup> *Id.* at p. 10.

<sup>57</sup> *Id.* at pp. 2-3, 56.



- ii. In their 2017 report “Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,” The National Academies of Science, Engineering and Medicine (NASEM) cited “heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some) and substantially increased prescribing” as contributors to the widespread availability and exposure to prescription opioids.<sup>58</sup>
- iii. The NASEM Report also found that diversion is a key contributor to increased exposure to prescription opioids. Prescription drugs are diverted to nonmedical use in several ways: (1) diversion before a prescription has been filled (*e.g.*, theft from production facilities or retail pharmacies), (2) diversion via the filling of a prescription (*e.g.*, pursuant to doctor shopping and high-frequency prescribers, etc.) and (3) diversion after a prescription has been filled (*e.g.*, by subsequent transfer or sale to a third party). “The DEA (2016b, p. 34) reports that in recent years, distributors in the United States disbursed 12-15 billion dosage units of opioid narcotics to retail-level purchasers, suggesting that total diversion is on the order of 2.5-4.0 billion dosage units.”<sup>59</sup> A *Washington Post* analysis of federal ARCOS data shows that from 2006-2014, more than 100 billion oxycodone and hydrocodone pills were delivered in the United States.<sup>60</sup> At the same rate of diversion reported by NASEM for the period it reviewed, that would represent diversion on the order of 15.8-25 billion pills during the nine year period from 2006-2014.
- iv. Likewise, decreased supply of addictive substances decreases exposure and risk of addiction and related harms. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number of Americans consuming and becoming addicted to alcohol.<sup>61</sup> (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam

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<sup>58</sup>National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*; 2017. doi:10.17226/24781, at pp. 40-41 (emphasis added).

<sup>59</sup> *Id.* at p. 223.

<sup>60</sup> Steven Rich, Scott Higham and Sari Horwitz *More than 100 Billion Pain Pills Saturated the Nation over Nine Years*, *Washington Post*, January 14, 2020.

<sup>61</sup> Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.

War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.<sup>62</sup>

- k. Opioids are different from other addictive substances for the following reasons:
  - i. They are sold as medicine, normalizing their use and propagating a misleading safety profile, with devastating consequences.
  - ii. They kill quickly, such that even a single exposure in an opioid naïve person can lead to death.
  - iii. They create a debilitating dependence such that painful withdrawal leads to a vicious cycle of drug-seeking and withdrawal, as discussed in Section §C.10 of this Report, below.

**3. Opioid prescribing began to increase in the 1980s and became prolific in the 1990s and the early part of the 21st century, representing a radical paradigm shift in the treatment of pain and creating more access to opioids across the United States.**

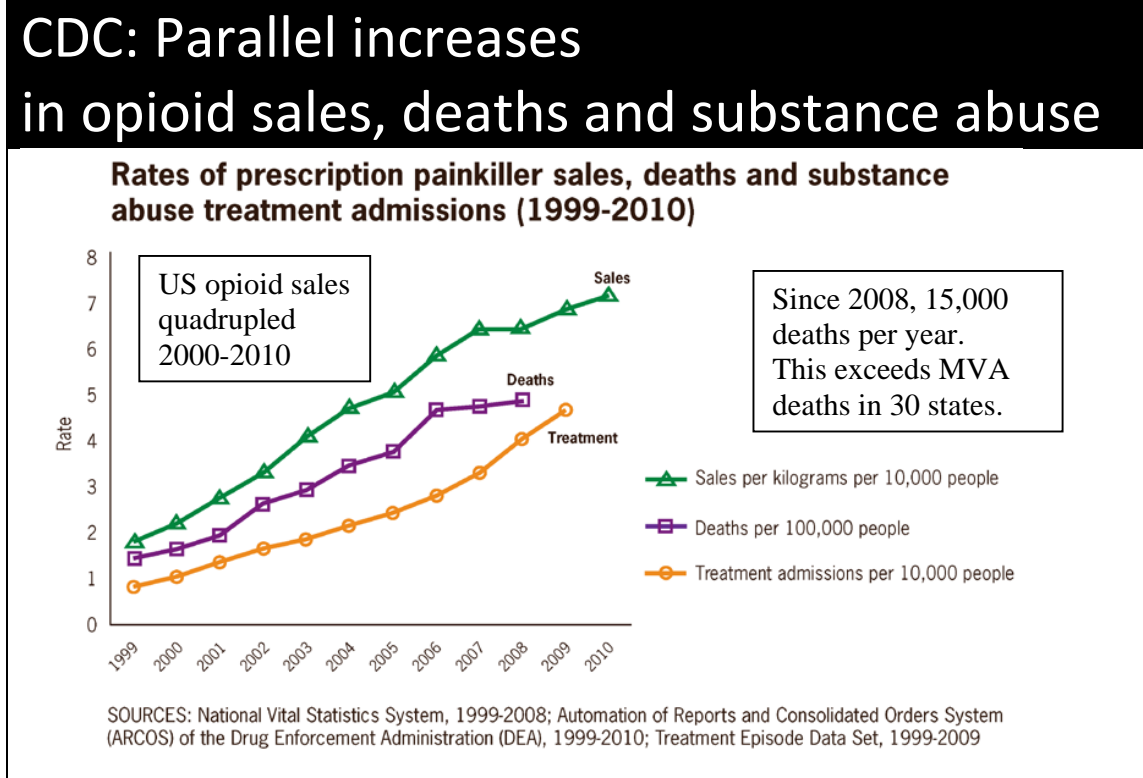
- a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life.<sup>63</sup> Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.
- b. Opioid prescribing quadrupled between the 1990s and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."<sup>64</sup>
  - i. From 1996 to 2011 there was a 1,448% increase in the medical use of opioids, with increases of 690% from 1995 to 2004 and 100% from 2004 to 2011. Over the same time period, opioid misuse increased more dramatically: 4,680% from 1996 to 2011, with increases of 1,372% from 1996 through 2004 and 245% from 2004 to 2011. The number of patients seeking treatment for opioid use disorder in this time period, not including heroin, increased 187%, whereas treatment-seeking increased 87% for heroin, 40% for cannabis, and decreased 7% for

<sup>62</sup> Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12\_Suppl.38, at p. 40.

<sup>63</sup> Meldrum ML. Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25). IASP Press; 2003, at pp. 195-199.

<sup>64</sup> Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s\\_cid=mm6043a4\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w), at p. 1489.

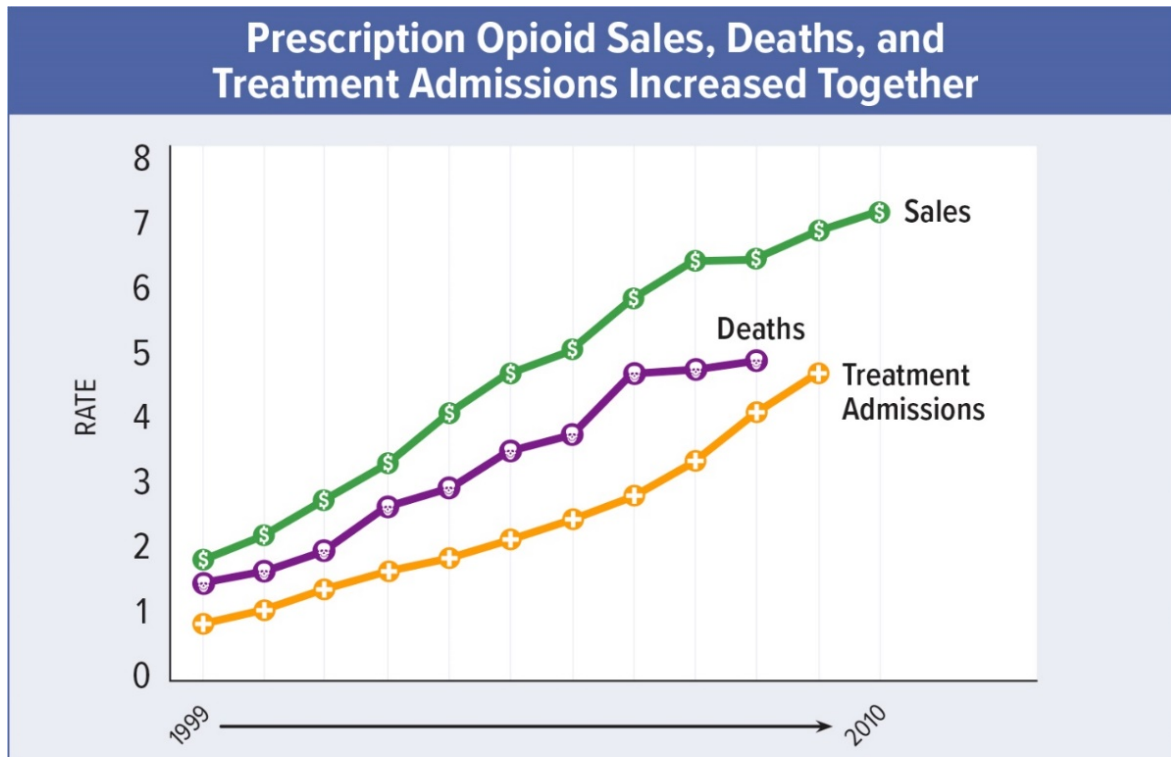
cocaine use disorder.<sup>65</sup> The increase in the medical use of opioid analgesics during this time period substantially contributed to increases in misuse and addictive use. The chart below,<sup>66</sup> based on official government data,<sup>67</sup> shows this close relationship, a simplified version of the same chart follows:



<sup>65</sup> Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician*. 2014, at p. E119.

<sup>66</sup> Reproduced from Sullivan MD, *et al.*, Opioid therapy for chronic pain in the US. *Pain* 2013; 154:S94-100, Fig.2.

<sup>67</sup> Centers for Disease Control and Prevention. *Prescription Painkiller Overdoses in the US infographic*. <https://www.cdc.gov/vitalsigns/painkilleroverdoses/infographic.html>, (last updated November 1, 2011).



SOURCE: CDC

- ii. A study by Paulozzi *et al*, published in 2006, analyzed death certificates from 1999-2002, and found that the most rapidly increasing category of death certificate-reported mortality was “opioid analgesic without heroin or cocaine,” which rose 129.2% in that time period, compared to deaths associated with heroin alone (without prescription opioids or cocaine), which rose only 23.7%, and cocaine alone, which rose 16%.<sup>68</sup> Paulozzi stated, “Overall, the relative increase in ARCOS opioid sales (76%) from 1999 to 2002 was consistent with the relative increase in opioid poisoning (95%).”<sup>69</sup>
- iii. The Paulozzi article also reported a 73% increase in opioid-analgesia-related emergency department visits between 1999-2002.<sup>70</sup> Paulozzi *et al*’s conclusion was that prescription opioids alone were the principal cause of death during the early years of the opioid epidemic,<sup>71</sup> with

<sup>68</sup> Paulozzi LJ, *et. al*. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiology and Drug Safety*. 2006;15:618-627, at p. 621.

<sup>69</sup> *Id.* at p. 624.

<sup>70</sup> *Id.*

<sup>71</sup> *Id.* at p. 626.

illicit drugs becoming more prevalent in later years, in part due to the higher cost and/or lesser availability of prescription opioids.

- iv. “By 2005, long-term opioid therapy was being prescribed to an estimated 10 million US adults. The volume of prescribed opioid analgesics was 100 MME [Morphine Milligram Equivalent] per person in 1997; in 2007, the MME per person had increased to almost 700 MME.”<sup>72</sup> By 2017, the level of MME had declined from its peak to 543.4 MME, which remains well over 5 times higher than the prescribing rate in 1997.<sup>73</sup>
- v. The number of long-term opioid users (daily for greater than 90 days) increased between 1999 and 2014. “Of all opioid users in 2013-2014, 79.4% were long-term users compared with 45.1% in 1999-2000.”<sup>74</sup> The increase in long-term use is important, because increased duration of use is also directly correlated with risk of addiction.<sup>75</sup>
- vi. Between 2006 and 2015, 66% of patients receiving an opioid prescription in an ambulatory (outpatient) care setting had a diagnosis of non-cancer pain, and 28% had no pain diagnosis at all. Only 5% of patients had a cancer-related pain diagnosis. Absence of a pain diagnosis was more common in visits where an opioid prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).<sup>76</sup>
- vii. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.<sup>77</sup> As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been

<sup>72</sup> Paulozzi LJ, Weisler RH, Patkar A a. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*. 2011;72(5):589-592. doi:10.4088/JCP.10com06560, at p. 589.

<sup>73</sup> Schieber LZ, Guy, GP, Seth P, *et al.* Trends and Patterns of Geographic Variation in Opioid Prescribing Practices by State, United States, 2006-2017. *JAMA Netw Open*. 2019;2(3):e190665, at p. 1.

<sup>74</sup> Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf*. 2017. doi:10.1002/pds.4278, at p. 526.

<sup>75</sup> Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals With Chronic Noncancer Pain. *Clin J Pain*. 2014;30(7):557-564, at p. 557.

<sup>76</sup> Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med*. 2018;169(12):892-894, at p. 892.

<sup>77</sup> Lembke *et al.*, “Use of Opioid Agonist Therapy”, fn.9, above, at pp. 990-991.

exposed to the risks of prescription opioids in recent decades, both within and outside the Medicare-eligible populations.<sup>78</sup>

- viii. In an evaluation of over one million Medicaid enrollees, one out of five pregnant women (21.6%) filled an opioid prescription. From 1992 to 2012, the proportion of pregnant women admitted to substance abuse treatment facilities that reported a history of prescription opioid addiction increased from 2% to 28%.<sup>79</sup>
- c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty, or region.<sup>80</sup>
  - i. In other words, opioid overprescribing is not merely the result of a small subset of so-called “pill mill” doctors, although such doctors do exist and have contributed to the current epidemic. Doctors across diverse medical specialties are prescribing more opioids.
  - ii. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, because there are more of them.<sup>81</sup>
  - iii. But the salient finding was that the increase in opioid prescribing is not explained by a minority of prolific prescribers alone. Rather, opioid prescribing has increased broadly across a variety of specialties.<sup>82</sup>
- d. A recent peer-reviewed publication evaluated prescriptions and diagnoses among enrollees in both commercial and Medicaid databases, and found that of 99,395 commercially insured and 60,492 Medicaid patients with an OUD diagnosis between 2005-2015, “most enrollees with OUD in the data had current opioid prescriptions.”<sup>83</sup> This supports the conclusion that prescription

<sup>78</sup> A 2020 study by Romman is consistent with our own findings, *see, e.g.*, Romman AN, *et al.* Opioid Prescribing to Medicare Part D Enrollees, 2013-2017: Shifting responsibility to pain management providers. *Pain Medicine*. 2020; 0(0): 1-9.

<sup>79</sup> Krans EE, Patrick SW. Opioid Use Disorder in Pregnancy: Health Policy and Practice in the Midst of an Epidemic. *Obstet Gynecol*. 2016 July; 128(1): 4-10, at p. 4. Opioid exposure during pregnancy increases the occurrence of Neonatal Abstinence Syndrome (NAS), a condition resulting in acute effects among newborns and long-term developmental delays. *See* discussion of NAS in Section §C.10.bb. of this Report.

<sup>80</sup> Chen et.al, “Distribution of Opioids”, fn.7, above, at p. 260.

<sup>81</sup> *Id.* at pp. 259-260.

<sup>82</sup> *Id.* at p. 260.

<sup>83</sup> Ali MM, *et al.*, Opioid Use Disorder and Prescribed Opioid Regimens: Evidence from Commercial and Medicaid Claims, 2005-2015. *J Med Toxicol*. 2019 Jul;15(3):156-168. doi: 10.1007/s13181-019-00715-0. Epub 2019 May 31, at p. 156. The authors state, “This suggests that opioids prescribed for pain continue to lead to the development of dependence and misuse.” *Id.* at 164. This statement supports my opinions concerning the “Gateway Effect,” as discussed in Section §C.9 of this Report.



opioids are intertwined with opioid addiction, and that the paradigm shift in medicine toward liberal opioid prescribing has been a major factor contributing to the increased supply which has fueled this opioid epidemic.

- e. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates, and greater than in other countries with comparable needs for analgesia.
  - i. The U.S. national average number of opioid prescriptions dispensed in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2020, the prescribing rate had fallen to its lowest in the 15 years for which the CDC had data, at 43 prescriptions per 100 persons (total of close to 143 million total opioid prescriptions).<sup>84</sup>
  - ii. However, prescribing rates in the United States are still greater than in the late 1990s, and greater than in other countries with comparable needs for analgesia. Further, in certain regions of the United States, opioid prescribing continues to remain very high, well above the national average. In 2020, according to the CDC, “In 3.6% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one.” And “some counties had rates that were nine times higher than” the overall dispensing rate of 43.3 prescriptions per 100 people.<sup>85</sup>
  - iii. A study of Georgia Medicaid enrollees from 2009 to 2014 found that the average number of opioid prescriptions increased over time across all demographic categories and that the average days supply, average daily dose, and average number of total incidence of potential inappropriate prescribing increased over time across all categories.<sup>86</sup> The authors noted that, “The implication of these trends (increased numbers of prescriptions, increased days supply, and increased daily dose) is that opioid use is increasing even with policy and societal pressure aimed at curbing marginal utilization.”<sup>87</sup>
  - iv. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and

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<sup>84</sup> Centers for Disease Control and Prevention. *U.S. Opioid Dispensing Rate Maps*.

<https://www.cdc.gov/drugoverdose/rxrate-maps/index.html>

<sup>85</sup> *Id.*

<sup>86</sup> Jayawardhana J *et al.* Opioid analgesics in Georgia Medicaid: trends in potential inappropriate prescribing practices by demographic characteristics, 2009-2014. *J Manag Care Spec Pharm.* 2018; 24: 886–894, at p. 5.

<sup>87</sup> *Id.* at p. 7.

over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. “Across all years of the study, annual opioid use prevalence was 14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries.”<sup>88</sup>

- f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.
  - i. Using International Narcotics Control Board figures, in 2019, the United States consumed 132,934 kilograms of 478,299 kilograms of opioids consumed globally (293,069.3 of 1,054,468.8 pounds), or 27.8 percent.<sup>89</sup>
  - ii. Using “defined daily doses,” the United States consumed the most opioids per unit population from 2013 to 2015: 47,580 doses of narcotic drugs were consumed per day per million people. Canada comes in second with 34,444 defined doses consumed per million people per day, and Germany in third with 30,796; Japan was 50<sup>th</sup> at 1,223 defined doses/day.<sup>90</sup>
  - iii. In summary, opioid prescribing was appropriately limited prior to the expanded uses that began in the 1980s and proliferated in the 1990s and beyond. As detailed in the following sections of this Report, such increased use of opioids was driven by misleading messages that downplayed risks and overstated benefits, and by widespread promotion, distribution, and dispensing that enabled overexposure to occur.

**4. The Pharmaceutical Opioid Industry contributed substantially to the paradigm shift in opioid prescribing through misleading messaging about the safety and efficacy of prescription opioids. The Industry disseminated these misleading messages through an aggressive sales force, key opinion leaders, medical school curricula, continuing medical education courses, seeding the medical literature, clinical decision support tools, professional medical societies, patient advocacy groups, the Federation of State Medical Boards, and The Joint Commission.**

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<sup>88</sup> Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *BMJ*. 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.

<sup>89</sup> International Narcotics Control Board for 2020, *Narcotic Drugs: Estimated World Requirements for 2021; Statistics for 2019*, at pp. 230-232. [https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2020/Narcotic\\_Drugs\\_Technical\\_publication\\_2020.pdf](https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2020/Narcotic_Drugs_Technical_publication_2020.pdf)

<sup>90</sup> *Id.* at pp. 226-228.



- a. Based on decades of prior experience with opioids, doctors had come to understand that, in most circumstances, opioids were too dangerous (and any long-term benefits too unproven) to be used other than to treat acute pain for short periods under direct supervision, or for end-of-life cancer pain. Thus, prior to the 1980's, opioids were prescribed sparingly, with the risk of addiction a primary consideration in the decision whether and under what circumstances to prescribe. Starting in the late 1990s, due to the Pharmaceutical Opioid Industry's aggressive and misleading promotion, opioids were prescribed in abundance with insufficient attention to, or appreciation of, the risks of addiction and overdose and the lack of reliable evidence of efficacy.
- b. The Pharmaceutical Opioid Industry targeted doctors and patients by creating an aggressive sales force, by promoting key opinion leaders, by infiltrating medical school and continuing medical education courses, by supporting professional medical societies, by influencing electronic medical record systems, and by co-opting medical watchdog organizations like the Federation of State Medical Boards and The Joint Commission to convince prescribers and the broader health care system that liberal opioid prescribing is based on science, and that failing to prescribe opioids is tantamount to forcing patients to live in pain. They misrepresented marketing as education and used flawed and biased studies to achieve this goal. These misrepresentations were transmitted to medical students, residents, and physicians, leading to a paradigm shift in opioid prescribing, such that opioids became first-line treatment for minor and chronic pain conditions. In fact, there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.<sup>91</sup>
- c. As stated by the National Academies of Sciences, Engineering and Medicine, "on the supply side, weak government regulations and aggressive and highly effective marketing tactics on the part of the pharmaceutical industry (manufacturers, distributors, pharmacies) and pain management advocacy groups (many of which were funded by the pharmaceutical industry) and physicians sparked a massive increase in opioid prescribing in the 1990s and 2000s and the subsequent rise in prescription opioid misuse, addiction and

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<sup>91</sup> As stated in a 2019 study, "The contribution of prescription opioids to the sharp rise in overdose deaths in the United States began in the late 1990's and is primarily an iatrogenic problem, driven by an increase in opioid prescribing for persistent pain. The drivers of this increase are complex, including factors within the health care system (eg, adoption of the pain scale as the fifth vital sign, aligning physician incentive payments with patient satisfaction, pharmaceutical industry marketing) and public expectations for pain treatment." Hedberg K, *et al.* Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority's opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at p. 219. As detailed in this section of the Report, the Pharmaceutical Opioid Industry promoted the "drivers" referenced in the quoted text, including the "fifth vital sign" and "patient satisfaction" based on pain scores.

overdose (Kolodny *et al.* 2015).”<sup>92</sup> The same NASEM report found that: “Drug distributors, dispensers, and *pharmacy chains* (e.g., Walgreens, CVS, Rite Aid) also *contributed to and profited from overprescribing through their failure to monitor and investigate suspicious opioid prescribing patterns* (Cuéllar and Humphreys, 2019; Hoffman, 2020).”<sup>93</sup>

- d. The Stanford-*Lancet* Commission stated that, “Perhaps the most important fact to remember about the opioid crisis is that, for some people, it brought not suffering but enormous wealth.”<sup>94</sup> Purdue Pharma, Insys Therapeutics, “Johnson & Johnson, Endo, Teva, and other opioid manufacturers also reaped substantial revenue from soaring prescription rates. Many pharmaceutical distributors also profited handsomely while knowingly making astonishingly large shipments of pills, which they were required to report to regulators but did not. And profit-seeking was not entirely external to the health care system: some hospitals, clinics, pharmacies, professional societies, and individual health-care professionals also enriched themselves.”<sup>95</sup> The Commission found that “the epidemic of opioid addiction and overdose emerged from, and is still to some extent being fueled by, legally prescribed opioids”<sup>96</sup> and that the opioid epidemic was fueled by aggressive opioid manufacturer marketing, including in-person sales detailing; large and small gifts; direct financial payments for endorsing industry products in lectures and case conferences; insertion of product promotions into electronic medical record systems; direct-to-consumer advertising of products to relieve side effects of opioids, although such advertising to consumers was not permitted for the opioids themselves; even the medical “education process has been corrupted by opioid manufacturers in various ways throughout the opioid crisis,”<sup>97</sup> and the “pharmaceutical industry engages in these [marketing] practices because they are proven to increase prescribing of their products.”<sup>98</sup>
- e. Aggressive Sales Force
  - i. As explained below, the Pharmaceutical Opioid Industry retained an aggressive sales force incentivized to target doctor’s offices and pharmacies to increase sales, thereby increasing the number of people exposed to opioids.

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<sup>92</sup> National Academies of Sciences, Engineering and Medicine (NASEM) 2021. *High and Rising Mortality Rates Among Working-Age Adults*. Washington, DC. The National Press. <https://doi.org/10.17226/25976>, at p. 240.

<sup>93</sup> *Id.* at p. 244. (emphasis added)

<sup>94</sup> Stanford-*Lancet* Commission, fn. 17, above, at p. 12.

<sup>95</sup> *Id.*

<sup>96</sup> *Id.*

<sup>97</sup> *Id.* at pp. 12-14.

<sup>98</sup> *Id.* at p.12.

- ii. In 2012, the pharmaceutical industry spent \$15 billion on face-to-face sales and promotional activity.<sup>99</sup> These face to face promotional activities rely primarily on sales representatives (drug reps) who market their products directly to doctors' offices and pharmacies.<sup>100</sup> The Pharmaceutical Opioid Industry uses a host of proven strategies to influence doctor prescribing, including but not limited to: a lucrative bonus system, sophisticated databases to target doctors who are already prolific prescribers with a large population of pain patients, intensive sales training to provide specific language for how to talk to prescribers, speakers' bureaus to disseminate promotional messaging to large groups of doctors all at once, free samples/coupons/vouchers for opioid drugs, branded promotional items such as "Oxycontin fishing hats, stuffed plush toys, and music compact discs," free meals,<sup>101</sup> and, in my experience, steaming cups of hot coffee delivered right to the office door.
- iii. The literature shows that these tactics work to increase prescribing of specific products. "Industry proponents assert that because physician detailer interaction raises awareness of new products, the practice benefits patients. However, no evidence exists to support this claim. In contrast, research suggests that physicians rely heavily on detailers for information and that the more doctors rely on commercial sources of information, the less likely they are to prescribe drugs in a manner consistent with patient needs. Information provided by detailers is often biased, and sometimes dangerously misleading. The reviews by Lexchin (1989; 1993) and Wazana (2000) correlate physician-detailer interactions with marked physician preferences for new products that hold no demonstrated advantage over existing ones, a decrease in the prescribing of generics, and a rise in both prescription expenditures and irrational and incautious prescribing."<sup>102</sup>
- iv. A 2018 study by Hadland *et al* found that marketing of opioid products across U.S. counties was associated with increased prescribing.<sup>103</sup>

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<sup>99</sup> Pew Charitable Trust, "Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients. (November 11, 2013). <https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients>

<sup>100</sup> *Id.*

<sup>101</sup> Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp. 221-222. *See also*, Pew, "Persuading the Prescribers", fn. 99, above.

<sup>102</sup> Katz D, *et al.* All gifts large and small: Toward an understanding of the ethics of pharmaceutical industry gift-giving. *American Journal of Bioethics*. 2010;10(0);11-17, at p. 12. Originally appeared in *American Journal of Bioethics*. 2003;3(3):39-46. (internal citations omitted)

<sup>103</sup> Hadland SE, *et al.* Association of Pharmaceutical Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing. *JAMA Internal Medicine*. 2018;178(6):861-863.

Although the authors cautiously described their findings as ‘associations’ rather than ‘causal associations,’ in a Reply to a Letter to the Editor of *JAMA Internal Medicine* concerning the 2018 publication, Hadland cited several traditional factors considered by epidemiologists to infer causality: (1) “temporality between exposure and outcome,” to ensure that “prescribing changes occurred after marketing was received;” (2) findings that were “consistent with other research showing that physicians who receive pharmaceutical industry payments prescribe more of the medications being marketed;” and (3) “dose-response,” with “each additional industry-sponsored meal associated with greater subsequent prescribing.”<sup>104</sup>

- v. Temporality, consistency, and dose-response are all among the factors cited in a seminal 1965 article by Sir Austin Bradford Hill, establishing a well-recognized methodology to determine causality between an intervention or exposure and an outcome.<sup>105</sup> Hadland also stated, “It is unlikely that pharmaceutical companies would invest so heavily in direct-to-physician marketing if it did not increase or at least maintain current levels of prescribing.”<sup>106</sup> See Section §C.13 below, for the role of the Bradford-Hill factors in this case.
- vi. A 2019 study by Hadland *et al.*, found that “across US counties, marketing of opioid products to physicians was associated with increased opioid prescribing and, subsequently, with elevated mortality from overdoses.” The authors go on to say that “Amid a national opioid overdose crisis, reexamining the influence of the pharmaceutical industry may be warranted.”<sup>107</sup>
- vii. A 2023 study of the long-term impacts of OxyContin marketing found that “Our results suggest that the mortality and morbidity consequences of OxyContin marketing continue to be salient more than twenty-five years later.”<sup>108</sup>
- viii. It is my opinion in light of the totality of evidence, including the parallel increases in sales, marketing, and opioid mortality over a 20+ year period, (see Sections §C.3, above, and §C.12 and §C.13, below) as well as the specific relationships documented by Hadland,<sup>109</sup> that there is a cause and effect relationship between promotion of opioids through

<sup>104</sup> Hadland SE, *et al.* In Reply. *JAMA*. 2018;178(10):1426-1427.

<sup>105</sup> Hill AB, The Environment and Disease. *Proceedings of the Royal Society of Medicine*. 1965;58(5) :295-300.

<sup>106</sup> Hadland SE, *et al.* In Reply. *JAMA*. 2018;178(10):1426-1427., above at p. 1426.

<sup>107</sup> Hadland SE, *et al.* Association of Pharmaceutical Industry Marketing of Opioid Products with Mortality from Opioid-Related Overdoses. *JAMA Network Open*. 2019;2(1):e186007, at p. 1.

<sup>108</sup> Dennett JM, Gonsalves GS. Early OxyContin Marketing Linked To Long-Term Spread Of Infectious Diseases Associated With Injection Drug Use. *Health Affairs (Project Hope)*, 2023. Advance online publication, at p. 1.

<sup>109</sup> *Id.*, see also Hadland SE, *et al.* Industry Payments to Physicians for Opioid Products, 2013-2015. *Am J Public Health*. 2017;107:1493-1495; Hadland SE, *et al.* Association of Pharmaceutical Marketing of Opioid Products to Physicians with Subsequent Opioid Prescribing. *JAMA Internal Medicine*. 2018;178(6):861-863.

false and misleading statements of low risk and substantial benefit, increased opioid prescribing, and opioid-related mortality.

ix. Endo

- A. A 2007 performance evaluation of an Endo sales representative demonstrates the effects of direct marketing to physicians: “one on one dinners and lunches have greatly attributed [sic] to your Opana [sales] growth...You utilizes [sic] the selling technology afforded to you by the Endo Selling model and engendering thoughts with your clients. I most recently observed this with Dr. Helms where you got him to see that he was too conservative in dosing Opana in the past and to agree to try Opana again on a patient he was seeing that very week.”<sup>110</sup>
- B. An August 16, 2007 Endo audio recording distributed to Endo sales representatives included a “success story” of a sales representative utilizing an Endo’s on-demand Lunch and Learn program with a “high decile Opana target” and included the comment that with “the successful application of this very valuable [Lunch and Learn] tool...I’m expecting to see these Opana ER prescriptions fly in!”<sup>111</sup>
- C. An Endo “2009 OPANA Brand Strategic Plan,” shows the importance of Endo’s sales representatives to their promotion of opioid products.<sup>112</sup> Endo targeted the highest volume prescribers, while also working to recruit new prescribers.<sup>113</sup>
- D. The Endo “2009 OPANA Brand Strategic Plan” focused on “the highest OPANA ER potential customers by adjusting targeting for greater sales call efficiency.” “Focus on PCPs [Primary Care Physicians] who act like pain specialists.” This “focus” was significant, because Endo’s Plan recognized that “Pain Specialists Are Most Productive.”<sup>114</sup> While pain specialists account for only 15% of the prescribers, they accounted for 30% of the prescriptions.<sup>115</sup> Endo advocated “targeting for more efficient deployment of resources on highest potential targets.”<sup>116</sup> This is relevant to the issue of “reverse causation.” Reverse causation in this context posits

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<sup>110</sup> ENDO-CA-00110112 at -0119

<sup>111</sup> ENDO\_ALAG-00465415

<sup>112</sup> ENDO-CHI\_LIT-00023217 (produced natively).

<sup>113</sup> *Id.* at \*15 and \*21.

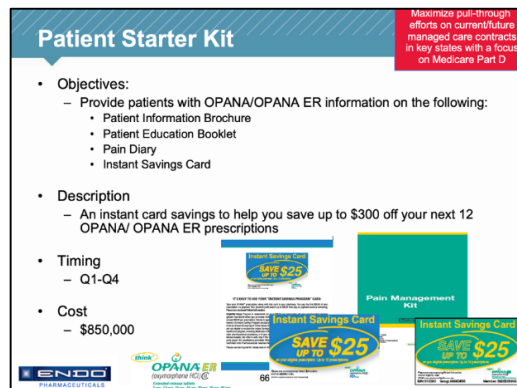
<sup>114</sup> *Id.* at \*15 and \*11.

<sup>115</sup> *Id.*, at \*11.

<sup>116</sup> *Id.* at \*31.

that the promotional efforts of the pharmaceutical industry were directed to the most prolific opioid prescribers because they were already prescribing more opioids. But this document makes it clear that Endo specifically targeted high prescribers because their promotional efforts to this group yielded even more opioid prescribing. Projected sales support in 2009 for Endo drug reps was more than \$3 million, indicating the value of the sales representatives to Endo's Strategic Plan to increase sales.<sup>117</sup>

- E. Not only were opioid drug reps encouraged to disseminate the same misleading messages about opioid risks and benefits as detailed in this report; they were also a source of free drugs via samples,<sup>118</sup> coupons, and vouchers, which in turn promoted easy access to opioids, a known risk for opioid addiction and overdose death. Endo promoted its Instant Savings Card (ISC) for Opana and Opana ER: "Save up to \$25."<sup>119</sup> This campaign boosted Endo's sales: "The ROI for the OPANA ER ISC Programs ranges from 1600-9700%."<sup>120</sup> By their own analysis, 20% of ISC cards were used for three or more months, "indicating increasing brand loyalty"<sup>121</sup> and also leading to ongoing exposure to opioids. As will be shown in subsequent sections of this report, the longer patients are on opioids, the more likely they are to become addicted to them. Endo also launched a "Patient Starter Kit" which included an OPANA ER Instant Savings Card:<sup>122</sup>



<sup>117</sup> ENDO-CHI\_LIT-00023217, at \*81. (produced natively).

<sup>118</sup> Pew Trust, "Persuading the Prescribers", fn. 99, above.

<sup>119</sup> *Id.* at \*66-67.

<sup>120</sup> *Id.* at \*67.

<sup>121</sup> *Id.*

<sup>122</sup> *Id.* at \*66.



- F. Endo business plans and reviews reported positive returns on its promotion of Opana ER and Percocet. A 2002 business review reported that the Percocet “sales message is having a positive impact on physicians,” and that “approximately 90%” indicate that they have prescribed the new strengths recently.<sup>123</sup>
- G. Emails from January 2012 state that Endo’s sales representatives were also provided with “non-branded” sales tools for Opana sales detailing, including Scott Fishman’s book “Responsible Opioid Prescribing” and Lynn Webster’s book “Avoiding Opioid Abuse While Managing Pain” which contained multiple misleading statements, as discussed in Sections C.4.j.iv, Appendix II (Fishman) and C.4.d.vii (Webster). Both Fishman and Webster were Industry KOLs who were paid to promote opioid use. Additionally, Endo sales reps were provided with “pharmacy locator sticky notes” and other handouts for health care providers.<sup>124</sup>
- H. It is striking that at the same time, January 2012, internal meeting minutes from the Opana ER Risk Management team stated that “The Team reviewed the 16 cases of misuse, abuse, dependence, overdose and death report for December 2011. It was noted that the trend in reports per 100,000 sales units has continued to increase. (Chart 2). In particular, there appears to be a fundamental change in the shape of the curve with the possibility of a ‘step function’ observed starting in July 2011.”<sup>125</sup> The minutes further state that “abuse and misuse of Opana and Opana ER continues to be a problem.”<sup>126</sup> The referenced chart of Opana misuse, abuse, dependence, overdose and death is reproduced below.<sup>127</sup> This evidence of correlation between sales of Opana and adverse Opana events is consistent with the CDC graph shown above,<sup>128</sup> and reinforces my opinion that there is a cause and effect relationship between the oversupply, exposure, and harms due to opioids, including Opana.

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<sup>123</sup> ENDO-OPIOID\_MDL-04927196 at \*20 (produced natively).

<sup>124</sup> ENDO-OPIOID\_MDL-00995017, at -5018.

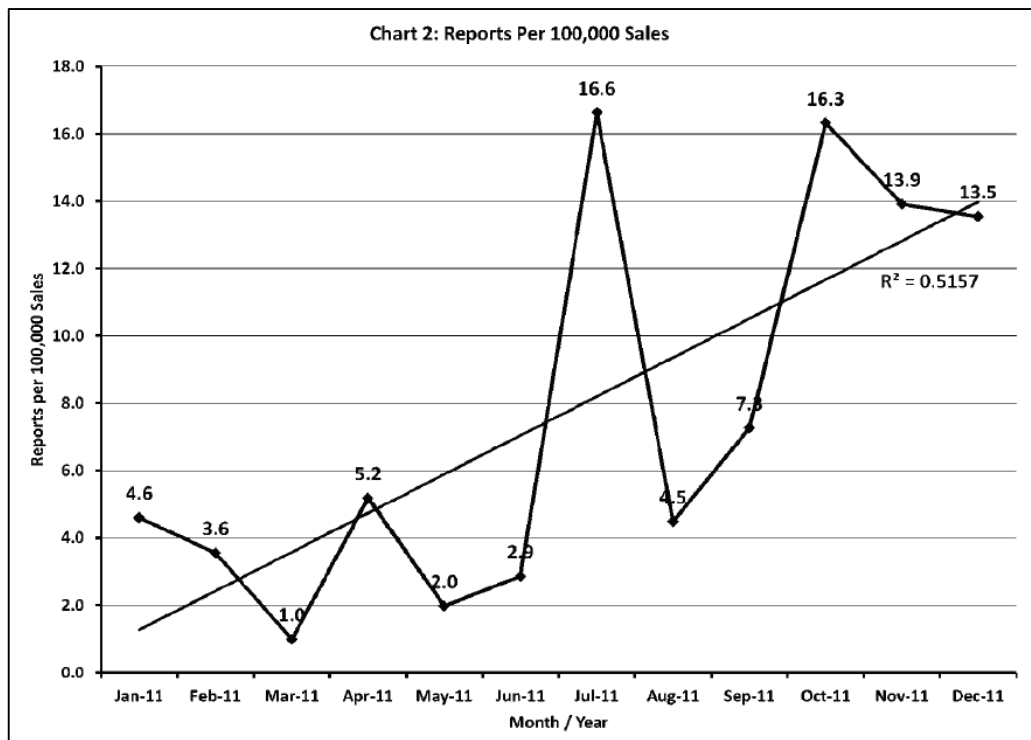
<sup>125</sup> ENDO-OPIOID\_MDL-00824629, at -4631.

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> See Section §C.3.b





I. A third party analysis prepared for Endo in July 2012 found that Endo's Opana ER marketing tactics drove 19% of total sales or \$72 million dollars, with sales force detailing accounting for \$45 million of that.<sup>129</sup>

x. Actavis/Allergan

- A. Allergan also marketed its products through an aggressive sales force. Deposition testimony and exhibits, summarized below, demonstrate that Actavis-trained sales personnel in positions of authority were unacceptably ill-informed about the addictive drugs they were promoting, yet nevertheless exacerbated the opioid epidemic by aggressive promotion of prescription opioids.
- B. Actavis coordinated with inVentiv, a contract sales organization (CSO), to employ a sales force for Kadian, an Actavis morphine sulfate product. Mark Killion was employed by inVentiv, as a Regional Business Director for Kadian, from

<sup>129</sup> ENDO-CHI\_LIT-00214471 at \*37 (produced natively).

May 2009 to December 2012.<sup>130</sup> In that capacity, Killion received sales training from Actavis,<sup>131</sup> and Killion, in turn, supervised between 9 and 12 area sales managers promoting Kadian in Texas and the Midwest region, as well as in the West region, including California.<sup>132</sup>

- C. Mr. Killion testified that he couldn't define what an opioid was,<sup>133</sup> couldn't explain tolerance,<sup>134</sup> or distinguish dependence from addiction.<sup>135</sup> While he recognized that Kadian is addictive<sup>136</sup> and was aware that we're in an opioid crisis driven by, in his words, "addiction of patients or people to opioid medications,"<sup>137</sup> he nevertheless testified to a sales force incentivized by quotas and bonuses to increase Kadian market share,<sup>138</sup> targeting high volume prescribers for non-cancer pain.<sup>139</sup>
- D. Killion testified that base salaries were paid on the basis of "sales performance," to provide an "incentive for sales results," and to "Maximize the sale of Kadian capsules."<sup>140</sup> Killion further testified that bonuses were paid on a percentage of a pre-specified sales quota, and that prescriptions were "dollarized," such that higher dosage Kadian had higher dollar value than lower dosage Kadian,<sup>141</sup> thereby incentivizing sales representatives to promote the more dangerous, higher dose product in order to earn greater bonuses.
- E. These "dollarized" prescriptions were particularly problematic when joined with the sales representatives' training that "Kadian does not have a ceiling or recommended maximal dose" and that Kadian could be titrated upward every other

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<sup>130</sup> Deposition of Mark Killion, *In Re: Texas Opioid Litig.*, No. 18-0358 (Supreme Court of Texas), September 11, 2020, at 10:2-22; (hereinafter, "Texas Killion deposition").

<sup>131</sup> *Id.* at 18:19-19:2; 21:16-24; 22:10-23:1.

<sup>132</sup> *Id.* at 10:9-11:11; Deposition of Mark Killion, *People of the State of California v. Purdue Pharma, L.P., et al.*, No. 30-2014-00725287-CU-BT-CXC, February 12, 2020, at 204:9-18 (hereinafter, "California Killion deposition").

<sup>133</sup> Texas Killion deposition, at 18:8-10. In response to a question as to whether he could define the term addiction "in detail," Killion answered, "I can't define the term, no." In light of Killion's answer, the phrase, "in detail," in the preceding question, is irrelevant.

<sup>134</sup> *Id.* at 60:21-61:17

<sup>135</sup> *Id.* at 63:25-64:11.

<sup>136</sup> *Id.* at 64:13-16

<sup>137</sup> *Id.* at 70:13-71:10

<sup>138</sup> California Killion deposition, at 79:5-85:22; Texas Killion deposition, at 24:11-28:15.

<sup>139</sup> Texas Killion deposition, at 34:24-35:15; 41:24-42:6

<sup>140</sup> California Killion deposition, at 79:5-83:21.

<sup>141</sup> *Id.* at 83:22-86:9.

day.<sup>142</sup> Actavis sales representatives were thus trained to promote higher and more dangerous doses of Kadian to doctors, while at the same time earning more bonus money by selling those higher and more dangerous doses.

- F. While Killion claims that he and Actavis sales representatives were instructed that promotion should include “fair balance” between risks and benefits,<sup>143</sup> that claim is refuted by the actual content of Actavis’ messaging, which consistently downplayed risks of addiction while overstating claimed benefits for chronic pain, as described in Appendix I of this Report.
- G. The Kadian sales force promoted a \$50 coupon for co-pay assistance to thousands of doctors and pharmacies.<sup>144</sup> The coupon was good for repeat use up to \$600 and available direct to consumers from an online website without a prescription.<sup>145</sup>
- H. The Kadian coupon program was expanded by Actavis to cover up to \$1,200 per year.<sup>146</sup> The explicit goals of the program to “Facilitate new therapy starts”<sup>147</sup> and “Increase the average length of therapy”<sup>148</sup> had the necessary consequence of increasing the population at risk of dependence, addiction, OUD, and overdose mortality.
- I. In January 2009, immediately after it acquired the Kadian brand, Actavis implemented a co-pay program to make the drug more affordable.<sup>149</sup> Kadian discount cards paid up to \$50 toward a patient’s co-pay and could be used twice a month. Because the typical co-pay was \$42, most discount card users paid nothing out of pocket.<sup>150</sup> Between January 2009 and May 2010, Actavis circulated approximately 150,000 discount

<sup>142</sup> Allergan\_MDL\_00026826 at -6832.

<sup>143</sup> California Killion Deposition, at 211:21-212:22.

<sup>144</sup> Texas Killion deposition, at 47:16-49:9 and 52:25-53:10 (testifying that Kadian co-pay assistance cards targeted to 9,000 physicians and 43,000 pharmacies); *see also* ACTAVIS0643304 (March 16, 2009 “Dear Pharmacist” email blast).

<sup>145</sup> *Id.* at 49:10-50:11; *see also*, Kadian website Co-Pay Assistance card request, [http://web.archive.org/web/20101205163516/http://kadian.com/en/co-pay\\_program.htm?WBCMODE=PresentationUnpublished](http://web.archive.org/web/20101205163516/http://kadian.com/en/co-pay_program.htm?WBCMODE=PresentationUnpublished) (last accessed October 22, 2020).

<sup>146</sup> ACTAVIS0237771; *see also* ACTAVIS0190235(Kadian “Save up to \$1,200” brochure)/

<sup>147</sup> *Id.* at -7775.

<sup>148</sup> *Id.*

<sup>149</sup> ACTAVIS0636185

<sup>150</sup> *Id.*

cards. Approximately 6-7% of the cards were used at least once,<sup>151</sup> representing between 9,000 and 10,500 individuals who were exposed to Kadian, an addictive drug, at little or no cost.

- J. The Actavis Co-Pay Program was significantly featured among the “Tactics” to promote Kadian in its sales representative training materials. For example, the sales representative materials of October 2011 cited the Co-Pay Program at multiple pages, and also described a one-page sheet called a “Shelf Talker” regarding the Co-Pay Program.<sup>152</sup> According to Killion’s testimony, the Shelf Talker was to be left with the Co-Pay Cards in doctors’ offices.<sup>153</sup> The Co-Pay Cards and the Shelf Talker combined to state that patients could save up to \$1200 per year, by re-using the same card to pay the first \$50 toward each prescription for up to 24 prescriptions over 12 months; and that 87% of managed care patients could pay zero dollars with the use of the Co-Pay Cards.<sup>154</sup> Thus, the Kadian Co-Pay Cards provided addictive drugs essentially “free” to patients for the first year, placing them at risk of opioid-related harms by the inducement of addictive drugs at low cost, or at no cost. This type of promotion is within the scope of behavior that the 2019 ASPPH report criticized.<sup>155</sup>
- K. Kadian sales representatives also bought lunches for health care professionals, and those purchased lunches were a vehicle for Kadian Sales representatives to make sales presentations to certain doctors.<sup>156</sup> As Hadland demonstrated, such gifts to doctors are directly correlated with their prescribing habits and their willingness to increase opioid prescribing.<sup>157</sup> Kadian sales representatives were also instructed to detail pharmacists to pass along information and to “ensure that patients get [Co-Pay] coupons.”<sup>158</sup>
- L. The effect of providing free or discounted addictive prescription drugs is seen in a December 2011 memorandum showing the impact of individualized attention by sales representative to

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<sup>151</sup> *Id.*

<sup>152</sup> California Killion Deposition Ex. 10, ALLERGAN\_MDL\_00026826 at 26863-26868; California Killion deposition at 138:9-19.

<sup>153</sup> California Killion deposition at 138:9-19; California Killion Deposition Ex. 10, Allergan\_MDL\_0026826 at 26865 and 26868.

<sup>154</sup> California Killion deposition at 129:1-140:11; California Killion Deposition Ex. 10, Allergan\_MDL\_0026826 at 26868.

<sup>155</sup> See discussion of 2019 ASPPH report at §C.2.j., above, and §C.4.r., below.

<sup>156</sup> California Killion deposition at 156:3-157:11.

<sup>157</sup> See discussion of Hadland at §C.4.e.

<sup>158</sup> California Killion deposition at 158:13-23.

doctors and pharmacists. The memo encouraged the sales rep to “continue to use your Kadian Co-Pay cards to gain access with your tough-to-see prescribers” and observed that a “great example of the impact you will have with your prescribers was your lunch with Dr. Zavarei in Anaheim. He was impressed that he now had a Kadian rep calling on him again. Your focus on the benefits of Kadian having a steady blood level through at 12 or 24 hour period was one that Dr. Zavarei easily bought into. He immediately mentioned he had patients that he would like to switch from generic MS Contin to Kadian”. The sales rep was also lauded for establishing a “great rapport” with a local pharmacist stocking the “Actavis generic version of Kadian” that “will pay dividends for Dr. Zavarei’s patients, and will make your new pharmacists contact at Ben’s Pharmacy extremely happy with his new business.”<sup>159</sup> According to Actavis’s own internal data, although Dr. Zavarei wrote no Kadian prescriptions in the year prior to being detailed, in January 2012, the month after the sales call, he wrote two prescriptions for the Actavis generic version of Kadian,<sup>160</sup> making him one of the “top 10 increases in prescription by prescriber” in that sales territory.<sup>161</sup>

xi. Watson

- A. Watson Pharma trained their sales people to promote Norco, a combination of the opioid hydrocodone and acetaminophen, by offering free product to doctors using the following language: “The outstanding offer is that Watson will send you 1 – 100 count bottle of each of these two [Norco] strengths at no charge,” with little or no information of risks of opioids, and no mention at all of the risks of misuse, addiction, and death.<sup>162</sup> (2001)
- B. In January 2002 Norco/Maxidone<sup>163</sup> Stocking Program Guidelines offered a “free goods promotion” as part of a program to “blitz all independent and small chain accounts that have not purchased Norco and Maxidone.”<sup>164</sup> Sales

<sup>159</sup> ALLERGAN\_MDL\_00396748 at -6749. Although this particular memorandum pertained to the Los Angeles area, it is likely that the same tactics had the same effect wherever else they were employed, since such tactics are employed for the purpose of increasing sales.

<sup>160</sup> ACTAVIS0673141

<sup>161</sup> ACTAVIS0791949

<sup>162</sup> ALLERGAN\_MDL\_03733190

<sup>163</sup> Maxidone was another hydrocodone/acetaminophen product.

<sup>164</sup> ALLERGAN\_MDL\_03733544 (emphasis in original)

representatives would receive \$50.00 sales credit for each order and were cautioned “Do not get into any type of discussion or dialog about efficacy or your opinions. Stick to the script. We are offering the pharmacist free product to put on their shelf so they can fill the Norco and Maxidone scripts. End of discussion.”<sup>165</sup>

- C. A March 2001 Watson sales training binder for Norco and Maxidone falsely stated that “Although physical dependence is common in patients receiving opioids for pain, addiction is quite rare. There is essentially no evidence that adequate administration of opioids for pain produces addiction.”<sup>166</sup> In fact, dependence is common in those who take opioids daily, and addiction affects up to one quarter of pain patients prescribed opioids. Further, in selling Norco, Watson instructed its sales force to use physician-directed sales tools including “leave-behind premiums – pens, pads, etc. and samples.”<sup>167</sup>

xii. Janssen

- A. Janssen used a similarly aggressive sales force and discount coupons to promote its opioid products. For example, Janssen deployed drug reps to target doctors directly to give away free fentanyl, an opioid that is 50 to 100 times more potent than heroin.<sup>168</sup> Janssen trained its sales representatives to promote the free fentanyl patches to doctors, with language as follows:

<sup>165</sup> *Id.* at 3545.

<sup>166</sup> ALLERGAN\_MDL\_03255938 at 5962.

<sup>167</sup> *Id.* at 5985.

<sup>168</sup> MCKMDL00334317. These free 5-packs of Duragesic were intended to provide 3 days per patch, for 15 days total, of continuous fentanyl exposure, which were essentially certain to create a predictable proportion of fentanyl-dependent consumers. Well-accepted data show that “the likelihood of chronic opioid use increase[s] with each additional day of medication supplied starting with the third day, with the sharpest increases in chronic opioid use observed after the fifth and thirty-first day on therapy, a second prescription or refill, 700 morphine milligram equivalents cumulative dose, and an initial 10- or 30-day supply. ... *The rate of long-term use* was relatively low (6.0% on opioids 1 year later) for persons with at least 1 day of opioid therapy, but *increased to 13.5% for persons whose first episode of use was for ≥8 days* and to 29.9% when the first episode of use was for ≥31 days. Although ≥31 days of initial opioid prescriptions are not common, approximately 7% do exceed a 1-month supply.” Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269, at p. 269 and 267. DOI: <http://dx.doi.org/10.15585/mmwr.mm6610a1> (emphasis added) These data show that Janssen’s free 15-day supply of Duragesic undoubtedly increased the number of long-term users of opioids, thereby increasing the occurrence of dependence and the likelihood of OUD, despite the lack of reliable evidence of long-term benefit.

- B. “Physicians may be more inclined to try Duragesic because patients are now able to ‘sample’ Duragesic free of charge.”<sup>169</sup>
- C. “Sell the coupons like they are a third product and close for action. ‘Dr. Smith, do you feel that the Duragesic coupons will be helpful to you and your patients when you are ready to convert to a long acting, because they can try Duragesic for free?’”<sup>170</sup>
- D. “Pull out one coupon from the pack and explain each section of the coupon .... Explain that one coupon is good for one free box of five patches, which is fifteen days of treatment. Remind the doctors that the coupon must be accompanied by a written prescription.”<sup>171</sup>
- E. “Display the coupons in a prominent place for easy access and to help remind the doctors of the program. It is very important to explain to the staff that you will replenish their coupon supply every month. This is very important so the doctors do not save the coupons for special patients.”<sup>172</sup>
- F. “Be very enthusiastic about the coupons! Make the physicians feel special because they are a part of only a select few that have the opportunity to participate in this coupon program.”<sup>173</sup>
- G. “I respond [to the doctor expressing reservations] by saying, ‘I believe that a patient in true chronic pain will try anything that you prescribe for them, because all the [sic] they want is pain relief. So, why not use a coupon that allows the patient to try Duragesic for free! You and the patient have nothing to lose.’”<sup>174</sup>
- H. Janssen’s business and tactical plans reported successful promotion of Duragesic. Its 2001 business plan for Duragesic reported a strong positive correlation between the number of promotion calls to pain specialists and the number of new Duragesic prescriptions they wrote, and that increasing the

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<sup>169</sup> JAN-TX-00066294.

<sup>170</sup> *Id.*

<sup>171</sup> *Id.*

<sup>172</sup> *Id.*

<sup>173</sup> *Id.* (emphasis in original)

<sup>174</sup> *Id.* at 6295.



number of calls from 1-2 in one quarter to 3-4 the next increased new Duragesic prescriptions by 14.3%.<sup>175</sup>

- I. Additionally, a 2005 Tactical Plan included review of Duragesic “e-detailing” and voucher programs which showed successful return on investment (ROI).<sup>176</sup> The plan reports that Janssen had a 1.5:1 return on a \$250,000 investment in an “internet-based promotional initiative” which had the objective of increasing “share of voice with high deciled physicians by delivering multi-wave DURAGESIC promotional messages via the internet.”<sup>177</sup>
- J. The voucher program was even more successful, showing a 29:1 ROI, or \$12.9 million return on a \$431,000 investment in a sample voucher program for “a box of 25 mcg or 50 mcg patches redeemed at a pharmacy for a free 15 day trial of Duragesic,” with the objective of initiating “trials of DURAGESIC immediately after short acting opioids earlier in the chronic pain treatment continuum for new patient starts.”<sup>178</sup>
- K. In addition to Duragesic, Janssen aggressively promoted Nucynta (tapentadol). Janssen did this in part by telling sales representatives that the more the Nucynta they sold, the more money they would make. A 2009 Janssen sales incentive and compensation plan informed sales people that “any NUCYNTA TRx’s generated in Q2 will pay \$40/TRx.”<sup>179</sup>

xiii. TEVA/Cephalon

- A. ACTIQ, a fentanyl lollipop, was FDA approved for “breakthrough cancer pain”. Cancer patients undergoing invasive treatments and suffering from potentially terminal disease are considered a separate category, for whom the benefits of potent, high dose opioids like fentanyl might outweigh the risks. However, ACTIQ was not approved for so-called breakthrough pain in any other population. Nonetheless, “Based on physician reporting, 90% of ACTIQ

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<sup>175</sup> JAN-MS-00310269 at \*11-12 (produced natively).

<sup>176</sup> JAN-MS-00310213 (produced natively)

<sup>177</sup> *Id.* at \*53.

<sup>178</sup> *Id.* at \*55.

<sup>179</sup> JAN-TX-00004105, at \*13 (produced natively)

use is for BTP outside of cancer, with the majority of use (55% of total) being for chronic back pain.”<sup>180</sup>

- B. Further, the 2005 ACTIQ marketing plan targeted existing prescribers, who were mostly prescribing for non-cancer pain.<sup>181</sup> Thus, as a result of an aggressive sales force, ACTIQ was sold to a much larger population of patients than those for whom it was approved. As a result, this larger population experienced increased risk of opioid addiction and overdose death.
- C. The 2007 Fentora marketing plan continued and extended the strategy of promoting transmucosal fentanyl for off-label use in patients with noncancer chronic pain, as previously set forth in the 2005 Plan, including but not limited to the following strategies: 1. “Differentiate from existing options,” 2. “Reinforce and *promote routine use*,” 3. “Promote *noncancer data*,” 4. “Promote superiority data,” and 5. “Promote *chronic pain management data*.”<sup>182</sup>



- D. Fentora’s 2007 marketing plan emphasized “Minimize risk of abuse, addiction and diversion” as a key strategy for Fentora as well as a critical success factor.<sup>183</sup> The plan stated that physicians’ fear of patient “abuse”, addiction and diversion of opioids should be part of “BTP Communication.”<sup>184</sup> Timothy Fortescue, a sales representative for Fentora, testified that “I can’t recall having a sales tool to educate or – or convince a

<sup>180</sup> TEVA\_CAOC\_00759630, at -9655.

<sup>181</sup> *Id.* at -9644-9946; 9655.

<sup>182</sup> TEVA\_MDL\_A\_00364495, at \*77. (produced natively; emphasis added).

<sup>183</sup> *Id.* at \*82, \*124, \*6.

<sup>184</sup> *Id.* at \*31.

doctor on” addiction or abuse.<sup>185</sup> Yet fentanyl, the active ingredient in Fentora, is one of the most addictive and deadly opioids.

- E. It is particularly troubling that the Fentora marketing plans sought to promote off-label use, given its FDA approved indication only in opioid-tolerant patients with cancer pain.<sup>186</sup> It is also clear from these documents that the off-label market constituted the lion’s share of the targeted market.
- F. Jacqueline Morrison, a sales representative and later area sales manager for Actiq and Fentora<sup>187</sup> testified about an October 2003 “Actiq Consultants Meeting”<sup>188</sup> wherein speakers presented on arthritis pain, migraine and chronic pain and attendees discussed their own clinical use of Actiq for chronic non-malignant pain, migraine/headache, acute pain and prior to physical therapy.<sup>189</sup> Morrison also testified that in September 2005, only 3% of Actiq prescriptions were being written by oncologists versus 27% written by primary care physicians.<sup>190</sup> According to Fentora’s 2007 marketing plan, 94% of Actiq prescribers were in specialties other than oncology.<sup>191</sup>
- G. I am familiar with defense experts’ positions that non-oncologists can treat patients who have cancer, but this theoretical possibility is refuted by defendants’ own data showing that *cancer accounted for only 8% of all the underlying conditions treated with Actiq*.<sup>192</sup> Morrison agreed

<sup>185</sup> Deposition Transcript of Timothy Fortescue. City and County of San Francisco et al. v. Purdue Pharma, LP et al. Case No.: 3:18-cv-07591-CRB. December 1, 2021. (hereinafter “Fortescue Deposition”), at 88:6-13

<sup>186</sup> “Tolerance” in this context means that the patient requires a higher dose to achieve the same effect. “Tolerance” does not have the same meaning that it would have in lay parlance, where tolerance means “the capacity to endure continued subjection to something, especially a drug, transplant, antigen, or environmental conditions, without adverse reaction.” (*see* <https://www.google.com/search?q=tolerance&oq=tolerance&aqs=chrome..69i57j0i433i512j0i67j0i433i512j0i512l6.4939j0j7&sourceid=chrome&ie=UTF-8>) Actiq and Fentora, which contain fentanyl, are highly potent, potentially lethal opioids that if administered to an individual who was not already opioid tolerant can be fatal. It is non-trivial that the drug was marketed to individuals for whom it presents a mortal threat.

<sup>187</sup> Deposition Transcript of Jacqueline Morrison. City and County of San Francisco et al. v. Purdue Pharma, LP et al. Case No.: 3:18-cv-07591-CRB. December 16, 2021, at 15:11-14. (hereinafter “Morrison Deposition”)

<sup>188</sup> Morrison Ex. 11, at TEVA\_CAOC\_13823272, *see also*: Fortescue Ex. 20.

<sup>189</sup> Morrison Deposition, at 143:23-148:5. *See*: Morrison Ex. 11, at TEVA\_CAOC\_13823271-272.

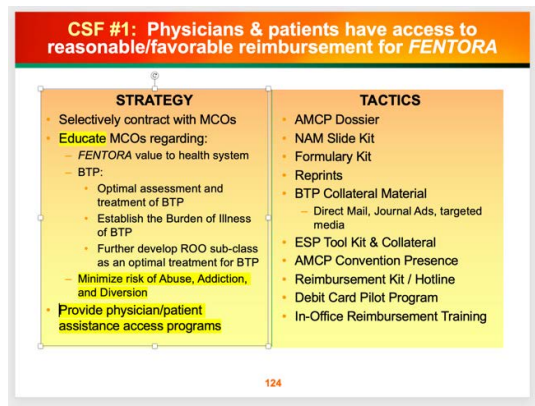
<sup>190</sup> Morrison Deposition, at 70:15-71:15. *See*: Morrison Ex. 6 (TEVA\_SF\_00002719), at \*38 (produced natively)

<sup>191</sup> TEVA\_MDL\_A\_00364495 at \*48.

<sup>192</sup> *Id.* at \*50.

that there would be a lot fewer sales of Actiq if doctors only prescribed it for cancer pain, as indicated.<sup>193</sup>

- H. A key strategy for Fentora in 2007, like for Actiq in 2005, was that Fentora would replace Actiq, oxycodone, hydrocodone, short acting morphine and short acting hydromorphone,<sup>194</sup> despite its limited approved indication for opioid tolerant patients with “breakthrough” cancer pain.
- I. TEVA/Cephalon planned to promote Fentora broadly and especially for extended indications beyond its FDA label in three ways: 1. An educational campaign to promote the notion of “breakthrough pain” in non-cancer patients, 2. Training its salesforce to “Minimize risk of Abuse, Addiction, and Diversion,” and 3. Providing physicians and patients with financial assistance to increase access to Fentora:<sup>195</sup>



- J. It was Fentora’s stated mission to “establish Fentora as the gold standard for BTP [breakthrough pain]” despite Fentora’s limited approved indication for breakthrough *cancer* pain (“BTCP”).<sup>196</sup> Fentora’s 2007 marketing plan described chronic pain prevalence far beyond the FDA-approved cancer indication, providing data on back pain, arthritic pain, neuropathic pain and even headache,<sup>197</sup> concluding that breakthrough pain was “an untapped market.”<sup>198</sup> That was an exaggeration, since the 2005 and 2007 Marketing Plans show

<sup>193</sup> Morrison Deposition, at 148:7-13.

<sup>194</sup> TEVA\_MDL\_A\_00364495 at \*188.

<sup>195</sup> *Id.*, at \*124. (emphasis added)

<sup>196</sup> *Id.*, at \*71

<sup>197</sup> *Id.*, at \*8.

<sup>198</sup> *Id.*, at \*34.

that the non-cancer breakthrough pain market was already being “tapped” significantly by Teva/Cephalon’s salesforce. Teva/Cephalon described the FDA-indicated approval for breakthrough pain in cancer patients as a “limited label” and “weakness” for Fentora.<sup>199</sup>

- K. At the February 2007 national sales meeting, Cephalon featured an Austin Powers-parody video which had the clear purpose of showing sales reps that Fentora could be used for all types of breakthrough pain, not just cancer. Timothy Fortescue, a sales representative who attended the meeting, agreed: “yes, I heard that message coming from ‘Austin Powers’. So, yes.”<sup>200</sup> In fact, the video didn’t even mention cancer.<sup>201</sup> Neither did a second James Bond parody video played at the same national sales meeting, which also talked about breakthrough pain without reference to the approved cancer indication.<sup>202</sup>
- L. Fentora’s 2007 marketing budget allocated \$6 million for speaker programs and workshops, \$6 million for Fentora sample coupons, and \$8.9 million for advertising and promotional materials.<sup>203</sup> Its tactics detailed “field driven promotional programs” including product vouchers,<sup>204</sup> sales materials and animation as well as “marketing driven promotional programs” including direct mail, journal advertising, website and conventions.<sup>205</sup> In the words of Timothy Fortescue, the sales representative “responsible for increasing sales of Fentora and Actiq in San Francisco Bay Area accounts” from 2006 through 2008,<sup>206</sup> “there were a variety of ways that the company tried to convey information with the purpose of increasing sales,” including medical information request responses, speakers programs, funding CMEs and conventions.<sup>207</sup>

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<sup>199</sup> *Id.*, at \*64.

<sup>200</sup> Fortescue Deposition, at 287:16-288:4.

<sup>201</sup> *Id.*, at 284:10-18.

<sup>202</sup> *Id.*, at 291:2-17.

<sup>203</sup> TEVA\_MDL\_A\_00364495, at \*131.

<sup>204</sup> In October 2006, more than 940 vouchers were redeemed for Fentora, representing 20% of total prescription sales for that month. 13% of the redeemed vouchers were for the highest strength, 800. See

TEVA\_MDL\_A\_00364495, at \*57, \*61-62.

<sup>205</sup> *Id.*, at \*125.

<sup>206</sup> Fortescue Deposition, at 17:13-20; 115:21-116:1.

<sup>207</sup> Fortescue Deposition, at 335:2-23. In the first quarter of 2008, Fortescue received almost \$20,000 in bonus for sales of Fentora and was the 17<sup>th</sup> highest in sales for Actiq nationwide in the first half of 2008, *see* 231:18-232:9 and 233:16-235:14.

- M. Teva/Cephalon's sales representatives had various ways to provide off-label information to prescribers. One method was to submit "a request to medical affairs to have information sent directly, which would remove the sales representative from the equation."<sup>208</sup> As an example, Fortescue testified about a March 2007 medical request form submitted on behalf of a doctor inquiring about Fentora's use in low back pain, an off-label use.<sup>209</sup> In response to the doctor, after acknowledging that Fentora was not indicated for the management of breakthrough pain in chronic non-cancer patients, the company provided information on two non-cancer studies of BTP associated with chronic low back pain.<sup>210</sup> The information provided to the physician indicated that Fentora was efficacious in low back pain patients.<sup>211</sup> Only "relatively minor side effects" were named in the materials.<sup>212</sup>
- N. Another option for responding to off-label questions was for the sales representative to set up a speaker program for the inquiring doctor.<sup>213</sup> According to the 2004 Actiq marketing plan, "Peer-to-peer selling is a highly effective means of developing Actiq prescribers and advocates," and sales-driven medication education programs were a "critical component" of Actiq promotional messaging.<sup>214</sup> In 2004 and "during the Actiq period", it was standard practice for Cephalon's paid speakers to provide off-label information during the question and answer periods of medical education programs.<sup>215</sup> Speakers were trained to handle off-label questions.<sup>216</sup> A January 2005 survey "to gain insights from our speaker bureau for the development of Cephalon sponsored events in

<sup>208</sup> *Id.*, at 55:6-16. *See also*: 65:15-66:18. *See also*: Morrison Deposition at 63:8-66:6.

<sup>209</sup> Fortescue Deposition, at 68:13-69:15.

<sup>210</sup> *Id.*, at 68:24-73:24. Doctors are permitted to prescribe for off-label uses. However, the Teva/Cephalon Plans demonstrate that promotion of Fentora for off-label non-cancer conditions and chronic pain was clearly intended, and highly successful; the mere fact of stating that the drug was not indicated for the condition does not eradicate the internal purpose to promote those very uses. As described below, the DOJ enforcement action against the company demonstrated that such subterfuge did not provide a defense to TEVA/Cephalon's purpose to promote off-label use.

<sup>211</sup> *Id.*, at 74:5-12. ("Q. All right. So, so basically they're, they're indicating that it is efficacious in low back pain patients. Is that your understanding of this section? A. I'll take a quick read. Q. Yep. A. (peruses document). Yeah, I – that's correct, that's my read of it.")

<sup>212</sup> *Id.*, at 74:18-75:6.

<sup>213</sup> *Id.*, at 55:20-24.

<sup>214</sup> TEVA\_MDL\_A\_09437449; TEVA\_MDL\_A\_09437452, at TEVA\_MDL\_A\_09437495 and TEVA\_MDL\_A\_09437452.

<sup>215</sup> Fortescue Deposition, at 59:22-16.

<sup>216</sup> Morrison Deposition, at 182:24-184:6. *See also* Morrison Ex. 6, TEVA\_SF\_00001234, at \*5 (produced natively), Morrison Ex. 27.

2005”<sup>217</sup> reported that Actiq speakers presented to prescribers on topics including chronic pain, breakthrough pain, neuropathic pain, non-cancer pain, back pain and migraine.<sup>218</sup>

- O. Speakers at these events included Jeffrey Gudin, a pain management doctor who was also a member of Purdue and Johnson & Johnson’s speaker programs<sup>219</sup> and conducted Actiq speaker training.<sup>220</sup> Gudin also appeared in a 2015 “Pain Matters” video, developed and paid for by Teva, which is still available today on YouTube.<sup>221</sup> In the video, Gudin states, “the benefits of effective treatment must be weighed against the consequences of inadequate analgesia.” This framing is not consistent with how we normally think about weighing risks and benefits. Typically, in the spirit of ‘first do no harm,’ the “benefits of effective treatment” would be weighed against the risks of harm from that treatment. Instead, Gudin juxtaposes benefits against “inadequate analgesia” thereby avoiding discussion related to the serious risk of harms from opioid use and speaking only to the harms of not prescribing enough opioids. Further, at slide 10 of his presentation, Gudin highlights “3.27% percent of patients being treated with chronic opioid therapy with high likelihood of abuse/addiction”<sup>222</sup> based on Fishbain (2008), an unreliable source for rates of opioid use disorder among chronic pain patients, as I discuss at §C.8.1, below. In fact, the best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.<sup>223</sup>
- P. In the first two months of 2007, Fentora speaker programs reached 5,570 prescribers nationally.<sup>224</sup> Cephalon’s speaker programs were cited by the U.S. Department of Justice in its 2008 criminal information filing and \$425 million civil settlement with Cephalon: “Cephalon employed sales representatives and retained medical professionals to speak to doctors about off-label uses of Actiq” and funded continuing

<sup>217</sup> Morrison Ex. 14, at TEVA\_FL\_00076573.

<sup>218</sup> Morrison Deposition, at 173:11-175:17. See also Morrison Ex. 14, at \*9. (produced natively)

<sup>219</sup> Gudin JA, *et al.* Risk, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013;125(4): 115-130, at p. 115.

<sup>220</sup> Morrison Ex. 21, at \*8 (produced natively)

<sup>221</sup> Pain Matters. “Evolving Roles Same Goals: Responsible Pain Management Clinical Presentations” [https://www.youtube.com/watch?v=\\_mMBBz2KQo8](https://www.youtube.com/watch?v=_mMBBz2KQo8) (posted December 4, 2015)

<sup>222</sup> *Id.*, at Slide 10 in the Pain Matter video, “What is the scope of intended abuse/addiction?”

<sup>223</sup> See discussion below, at §C.8.

<sup>224</sup> TEVA\_MDL\_A\_00364495, at \*61.



medical education programs “to promote off-label uses of its drugs, in violation of the FDA’s requirements.”<sup>225</sup> The Department of Justice found that “From 2001 *through at least* 2006, Cephalon was allegedly promoting the drug for non-cancer patients to use for such maladies as migraines, sickle-cell pain crises, injuries, and in anticipation of changing wound dressings or radiation therapy. Cephalon also promoted Actiq for use in patients who were not yet opioid-tolerant, and for whom it could have life-threatening results.”<sup>226</sup>

- Q. According to the Department of Justice, “Cephalon instructed the Actiq sales representatives to focus on physicians other than oncologists, including general practitioners, and to promote the drug for many uses other than breakthrough cancer pain.”<sup>227</sup> Teva/Cephalon sales Area Manager Morrison highlighted “top Actiq writers and high writers for pure short acting opioids” as possible sales targets, noting that “Since you get paid on dollar volume we are most interested in how many units they are writing and at what doses. The price of the unit goes up with the dose.”<sup>228</sup> Sales representative Fortescue testified that his approach “was look in my database and see which physicians in this territory are prescribing Actiq, and that was – that was who I saw.”<sup>229</sup> These are important admissions because it shows that Actiq sales representatives promoted Actiq to existing prescribers, indifferent to prescriber specialty or patient diagnosis. In 2006, Fortescue was the 10<sup>th</sup> highest of 100 sales reps nationally for Actiq and Fentora.<sup>230</sup> Fortescue detailed Fentora to doctors with specialties that included anesthesiology, pain management, physical medicine and rehabilitation, neurology primary care, nurses, pharmacists and oncology.<sup>231</sup> While Fortescue recalled that “it was very difficult to access the oncologists. And by ‘access’, it means to get a meeting”<sup>232</sup> he was nevertheless appointed as an area sales trainer, with an increased salary, in the same month.<sup>233</sup>

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<sup>225</sup> Fortescue Deposition, Ex. 46, at TEVA\_MDL\_A\_11436749

<sup>226</sup> *Id.*, at TEVA\_MDL\_A\_11436748-49. (emphasis added)

<sup>227</sup> *Id.*, at TEVA\_MDL\_A\_11436749.

<sup>228</sup> Morrison Ex. 5. *See also*: Morrison Deposition, at 38:20-41:8.

<sup>229</sup> Fortescue Deposition, at 327:11-23.

<sup>230</sup> *Id.*, at 21:2-8.

<sup>231</sup> *Id.*, at 84:10-85:10.

<sup>232</sup> Fortescue Deposition, at 214:20-215:3.

<sup>233</sup> Fortescue Deposition, at 130:12-131:11.

- R. Teva continued to educate its sales force with misleading messages about opioids through at least 2018.<sup>234</sup> A “Fentora PPLS Disease State Module” learning system for sales training stated that “in general, patients in pain do not become addicted to opioids.”<sup>235</sup> In fact, 10-30% of patients prescribed opioids will become addicted, based on the 2015 Vowles study, as discussed below at §C.8. Moreover, Teva’s sales training manual stated that “exposure to a potentially addictive drug, such as an opioid, does not necessarily result in addiction”<sup>236</sup> in contrast to the CDC’s August 2017 statement that “anyone who takes prescription opioids can become addicted to them.”<sup>237</sup>
- xiv. The above-described evidence makes it clear that promotion of opioids to prescribers and their staff is a highly effective strategy for increasing opioid sales. Given the inherently addictive potential of opioids and the current opioid epidemic, such promotional activities should not be allowed.
- xv. In February 2018, a news release announced that Purdue Pharma “cut its sales force in half and will stop promoting opioids to physicians, following widespread criticism of the ways that drugmakers market addictive painkillers.”<sup>238</sup> This decision on the part of Purdue Pharma was tacit acknowledgement of direct-to-physician/pharmacy marketing as a major driver of the opioid epidemic.
- xvi. In 2019, the ASPPH recommended stopping marketing of opioid medications: “Along with revisions in opioid drug labeling to discourage long-term use, federal regulations must be changed to prohibit (or strictly limit) the marketing of opioids to physicians and health systems....”<sup>239</sup> I agree that the aggressive marketing of addictive drugs, as described above, was never appropriate, and particularly improper when based on false and misleading messages of safety and efficacy. Though long overdue, the ASPPH recommendations should be implemented going forward.

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<sup>234</sup> Document metadata states that this May 2017 document was modified and in use on June 27, 2018.

<sup>235</sup> TEVA\_MDL\_A\_01135946, at -6005

<sup>236</sup> TEVA\_MDL\_A\_01135946, at -6005 and -6009

<sup>237</sup> CDC, “Prescription Opioids”, fn. 51, above. *See also* 2013 article stating “The most important risk factor for opioid analgesic-associated dependence or overdose is not a feature of any individual patient but simply involves receiving a prescription for opioids.”, fn. 52, above.

<sup>238</sup> *OxyContin maker stops promoting opioids, cuts sales staff*, Reuters, February 10, 2018, <https://www.reuters.com/article/us-usa-opioids-purduepharma/oxycontin-maker-stops-promoting-opioids-cuts-sales-staff-idUSKBN1FU0YL>

<sup>239</sup> ASPPH, “Bringing Science to Bear”, fn.24, above, at p. 11.

## f. Key Opinion Leaders

- i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits and minimize the risks.<sup>240</sup>
- ii. These ‘key opinion leaders’ and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled “Addiction Rare in Patients Treated with Narcotics.”<sup>241</sup> Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase “less than 1% get addicted,” based on this one data point, was used in opioid manufacturers’ branded advertisements and other promotional materials. (See Appendix I on promotional material.)
- iii. Significantly, the population in question in the Porter and Jick article is described as “hospitalized,” and receiving at least one dose of an opioid, without any reference to the size of the dose or range or duration of exposure. There is no reasonable basis to compare the risk of addiction among hospitalized patients who may have received only a single dose or short-term course of opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse.
  - A. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the “rarity” of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids.
  - B. A 2017 study reported in the *New England Journal of Medicine* found that the Porter and Jick letter had been cited 608 times,

<sup>240</sup> Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. (MDL No. 2804 Saper Dep. Ex. 6, at pp. 3-4).

<sup>241</sup> Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.

compared to a median of 11 citations to other letters published contemporaneously.<sup>242</sup> The authors stated: “In conclusion, we found that a five-sentence letter published in the Journal in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy. In 2007, the manufacturer of OxyContin and three senior executives pleaded guilty to federal criminal charges that they misled regulators, doctors, and patients about the risk of addiction associated with the drug. Our findings highlight the potential consequences of inaccurate citation and underscore the need for diligence when citing previously published studies.”<sup>243</sup>

- C. The following are examples of opioid manufacturer-sponsored, inappropriate and misleading reliance upon the Porter and Jick letter:
- I. In 1996, a Purdue Frederick-funded study reported that: “In three studies involving almost 25,000 patients without a history of drug dependence, there were only 7 cases of iatrogenic addiction.”<sup>244</sup> (Citing Porter and Jick and 2 other inapplicable studies by Perry and Medina, discussed in this Report at Section §C.4.f.iv-v, below). Moulin *et al.* described the risk of addiction as “negligible.”<sup>245</sup> Purdue Frederick is listed as a grant supporter of the Moulin article.<sup>246</sup>
  - II. In 1997, Purdue published “I Got My Life Back” a brochure and video promoting a “less than 1%” addiction rate, citing to Porter and Jick (1980).<sup>247</sup>
  - III. In 1998, a Janssen-funded study reported that a “low risk of iatrogenic psychological dependence has been

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<sup>242</sup> Leung PTM, *et al.* A 1980 Letter on the Risk of Opioid Addiction. *N Engl J Med.* 2017; 376:2194-2195, at p. 2194

<sup>243</sup> *Id.* at pp. 2194-2195.

<sup>244</sup> Moulin DE *et al.* Randomised trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147, at p. 143.

<sup>245</sup> *Id.* at p. 147.

<sup>246</sup> *Id.*

<sup>247</sup> PKY183063227 (brochure); PPLPC009000022561 (video transcript) (emphasis added)

observed in patients without a history of substance abuse” citing to Porter and Jick (1980).<sup>248</sup>

- IV. A 2001 Janssen presentation, “Optimizing Chronic Pain Management with Duragesic,” cites Porter and Jick (1980) for “low” risk of addiction in non-addicts and states that “the potential for addiction is in the patient, not the opioid.”<sup>249</sup>
- V. In 2001, an Endo-sponsored KOL (Dr. Covington, Cleveland Clinic) presentation and handout titled “Opioid maintenance in chronic non-malignant pain” concluded that “Iatrogenic addiction in treatment of acute pain is *virtually nonexistent*” citing to Porter and Jick (1980)<sup>250</sup>
- VI. In 2002, a Cephalon annual sales meeting presentation entitled, “The Myth of Addiction” concluded there was a “0.06% chance of becoming addicted” citing to Porter and Jick,<sup>251</sup> and directed its sales force: “Never Refer to Addiction when talking about opioids – especially Actiq!”<sup>252</sup>
- VII. Speaker’s notes from a 2003 Endo advanced sales training presentation state that “The occurrence of addiction as a result of opioid use for pain relief is extremely rare. Several studies have concluded that the risk is far less than 1%,” citing to Porter & Jick (1980).<sup>253</sup>
- VIII. The 2008 TEVA Fentora Learning System cite to Porter and Jick: “In one survey of patient [sic] taking opioids for severe pain, only four of 11,882 patients developed addiction. [APA, 2005, 2]”<sup>254</sup>
- IX. These examples demonstrate the point made in the 2017 *NEJM* article, that the Porter and Jick Letter was “heavily and uncritically cited as evidence that addiction

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<sup>248</sup> Dellemijn PLI, *et. al.* Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of Pain and Symptom Management*. 1998;16(4):220-229, at pp. 227-228. (emphasis added)

<sup>249</sup> JAN-MS-00653403 (December 14, 2001), at \*66 (produced natively).

<sup>250</sup> ENDO-OPIOID\_MDL-02002494; ENDO-OPIOID\_MDL-02002495 at slides 4-5 (emphasis added)

<sup>251</sup> TEVA\_AAMD\_00791885 at 1901-1902 (emphasis added)

<sup>252</sup> TEVA\_AAMD\_00791885 at -1887

<sup>253</sup> ENDO-OPIOID\_MDL-02356776 (produced natively), at \*57.

<sup>254</sup> TEVA\_MDL\_A\_00890305, at -0351.

was rare with long-term opioid therapy,” and “contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy.”<sup>255</sup>

- iv. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.<sup>256</sup> Burn debridement, consisting of the removal of dead tissue to promote healing, is a procedure carried out in a hospital setting. Mean administered morphine during the procedure was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after debridement, no details were provided regarding dose or duration, and burn healing is inherently a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes and did not use rigorous methodology to study this outcome.
- v. Opioid manufacturers and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.*, in support of the claim that risk of addiction was low.<sup>257</sup> Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. Thirty-eight of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and six were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, “Eight were dependent; six physically addicted, two psychologically dependent and two were abusers . . . . There is danger of dependency and abuse in patients with chronic headaches.” Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and ‘abuse’ not consistent with other studies or with DSM criteria of any edition; however, the finding that two

<sup>255</sup> Leung, “A 1980 Letter”, fn. 242, above, at p. 2194.

<sup>256</sup> Perry S, Heidrich G. Management of pain during debridement: A survey of U.S. burn units. *Pain*. 1982;13(3):267-280, at 267-77.

<sup>257</sup> Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain*. 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

patients were “psychologically dependent” would generally have been considered equivalent to a diagnosis of “addiction” at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators’ likelihood of identifying aberrant behavior.

- vi. Dr. Russell Portenoy, former chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York City, was a key opinion leader for opioid manufacturers. Between 1997 and 2012, Dr. Portenoy received nearly \$29,000 in direct payments from Janssen and its parent Johnson & Johnson (J&J), including \$16,940 for “sponsored research”.<sup>258</sup> Dr. Portenoy spread his pro-opioid messages as President of the American Pain Society, and as a member of the boards of the American Pain Foundation and the American Pain Society, organizations that received funding from the Pharmaceutical Opioid Industry.<sup>259</sup> The many hundreds of thousands of dollars in Pharmaceutical Opioid Industry payments to individuals such as Dr. Portenoy are evidence of Industry support for “key opinion leaders” whose work was used by the Industry to encourage opioid prescribing through aggressive misrepresentation of risks and benefits.<sup>260</sup>

- A. In 1986, Drs. Russell Portenoy and Kathleen Foley published a retrospective case series of 38 patients with chronic pain.<sup>261</sup> Portenoy and Foley’s review does not constitute a high level of scientific evidence. It did not include a large number of patients.<sup>262</sup> There was no comparison group taking a placebo or getting some other treatment for pain, such as physical therapy or non-opioid medication.<sup>263</sup> It was retrospective rather than prospective, meaning the authors asked patients to recollect past experiences, biased by recall effects, rather than soliciting their reactions going forward in real time. Nonetheless, they concluded “opioid maintenance therapy

<sup>258</sup> JAN-MS-00000001 at 0008.

<sup>259</sup> Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶¶ 37-40.

<sup>260</sup> Senate Homeland Security and Gov Affairs Comm, 116th Cong., Report on Fueling an Epidemic Report Two: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups (2018) at pp. 10-11, <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

<sup>261</sup> Portenoy RK, Foley KM, Chronic Use of Opioid Analgesics in Non-Malignant Pain: report of 38 cases. *Pain*. 1986;25:171-186.

<sup>262</sup> *Id.* at pp. 172-173. Patients reviewed were derived from two separate studies and only 19 patients were under treatment at the time of the study.

<sup>263</sup> *Id.*



initiated for the treatment of chronic non-malignant pain can be safely and often effectively continued for long periods of time.”<sup>264</sup> The statement represented a departure from previous practice, in which opioids were used almost exclusively for acute (after surgery or injury) and palliative pain (at the end of life). Portenoy and Foley went on to say that their review suggested that opioid medications can be used in this manner “with relatively little risk of producing the maladaptive behaviors which define opioid abuse.”<sup>265</sup> Yet in the 19 patients they “reviewed in detail,” one developed “psychological deterioration” and was hospitalized, where “opioid intake was rapidly increased without medical approval,” and the other appeared to be diverting prescribed opioids: “the patient appeared to require high doses of methadone for pain relief. After several months, a plasma methadone level revealed almost no circulating drug.”<sup>266</sup> The authors ignored these adverse outcomes when they stated, “There were no episodes of clinically significant adverse effects from the use of opioids.”<sup>267</sup>

- B. Portenoy’s co-author Foley stated in a subsequent 2011 letter to the editor, “We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect.”<sup>268</sup> This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED), putting them at high risk for opioid-related morbidity and mortality. Meanwhile, there is no reliable evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.
- C. Edlund *et al.* state, “Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk

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<sup>264</sup> *Id.* at p. 178.

<sup>265</sup> *Id.* at p. 184.

<sup>266</sup> *Id.* at p. 177.

<sup>267</sup> *Id.*

<sup>268</sup> Foley KM, Fins JJ, Inturrisi CE. A true believer’s flawed analysis. *Arch Intern Med.* 2011. doi:10.1001/archinternmed.2011.166, at p. 867.

increases substantially.”<sup>269</sup> The odds of developing an OUD in those exposed to opioids for 90 days or more, compared to those not exposed (odds ratio), are as follows: For low dose (1-36 MMEs per day), the odds ratio was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) the odds ratio was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) the odds ratio was 122.45 (95% CI = 72.79, 205.99).<sup>270</sup> Another way to say this is that patients exposed to 120 MMEs of opioids for 90 days or more, were 122 times more likely to develop an opioid use disorder within the year than those not exposed to opioids.

- D. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure, the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer from opioid use disorder than patients who were not prescribed opioids.
- E. In 2011, Dr. Portenoy conceded that there was no reliable evidence to support the statement that opioids are ‘low risk.’ In a taped interview Dr. Portenoy described his promotion of opioids in the 1990s and early 2000s as follows: “I gave so many lectures to primary care audiences in which the Porter and Jick article<sup>271</sup> was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn’t before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind*.”<sup>272</sup> (emphasis added). Dr. Portenoy’s statement supports my opinion that there was no reliable evidence that opioids are low risk.

- vii. Dr. Lynn Webster, a key opinion leader and paid consultant for the opioid manufacturing defendants, wrote a book called “Avoiding

<sup>269</sup> Edlund, *et al.*, “Role of Opioid Prescription,” fn.75, above, at p. 561,

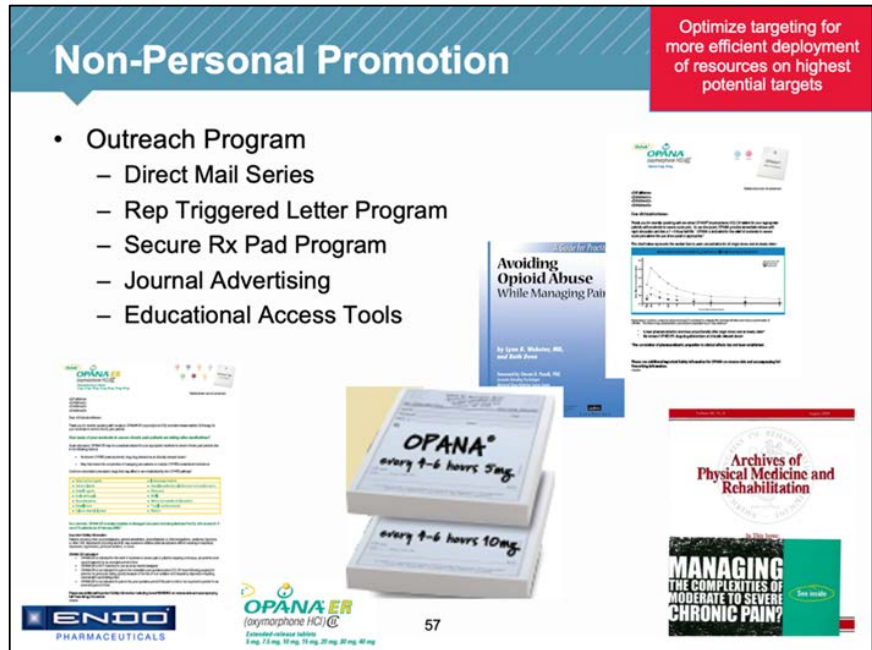
<sup>270</sup> *Id.* at p. 559-60. As shown in Table 3 at p.561, based on Edlund’s data, the OR with increasing dose and duration is far greater than the OR for other factors, such as prior substance use disorders or psychiatric diagnoses.

<sup>271</sup> Porter and Jick, “Addiction Rare,” fn. 241, above.

<sup>272</sup> Lurie J., *Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong?* Mother Jones. <https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/>.

Opioid Abuse While Managing Pain.” This book was used by Endo to promote increased sales of Opana by distributing it to physicians and pharmacies.<sup>273</sup>

- A. Webster’s book was featured in Endo’s “2009 OPANA Brand Strategic Plan,” as shown below.<sup>274</sup>



- B. Webster’s book contains many of the misleading messages about opioids that contributed to the oversupply, including that opioids are evidence-based treatment for chronic pain (they are not), and that addiction is rare (it is not) in individuals treated by a doctor with opioids for chronic pain.<sup>275</sup> In reality, every one of the following statements in the Webster book is false, misleading, unsupported by, or directly contradicted by scientific evidence:

- I. Webster wrote, “In a world with few alternatives, opioids remain the best treatment available for many chronic pain conditions and are the first choice of therapy for acute and postoperative pain.”<sup>276</sup> In fact,

<sup>273</sup> END00666533.

<sup>274</sup> ENDO-CHI\_LIT-00023217 (produced natively), at \*57. Alongside Webster’s book, note the many other methods Endo used to target prescribers: “Direct Mail Series,” “Rep Triggered Letter Program,” “Secure Rx Pad Program” (branded with the company’s opioid products, in this case “OPANA”), Journal Advertising,” and “Educational Access Tools” (such as the sad-face/happy-face Pain Evaluator used by Endo and described at §C.4.j.).

<sup>275</sup> Webster, Lynn. *Avoiding Opioid Abuse While Managing Pain*. Sunrise River Press, 2007, see ENDO-CHI\_LIT-00538705, at -8725.

<sup>276</sup> *Id.* at -8713.

opioids are not evidence-based treatment for chronic pain and work no better than Tylenol while incurring many more risks to the individual and the public health. Although opioids do work short term for acute pain, they are not always the “first choice of therapy” for acute or postoperative pain. Some individuals don’t tolerate opioids and even short term exposure increases the risk of persistent and addictive use. In fact, recent research has determined that opioid-sparing protocols provide equivalent pain relief and fewer risks with non-opioid analgesics.<sup>277</sup>

- II. Webster wrote, “Opioids offer safe, effective treatment for many chronic pain conditions and pose little risk of addiction for most patients who take them to control pain.”<sup>278</sup> As above, this statement is false. Opioids are neither safe nor effective for chronic pain and pose significant risk of addiction and overdose death.
- III. Webster wrote, “Addiction can usually be predicted.”<sup>279</sup> Not true. There is no way to tell who will and will not become addicted to opioids through a doctor’s prescription. Risk factors like family or personal history of mental illness incur less risk than simple exposure to opioids at high doses for long duration (three months or greater).<sup>280</sup> Further, the Opioid Risk Tool, created by Dr. Webster and widely used and promoted to screen out patients vulnerable to addiction, has been shown in follow up studies to be “no better than chance” at predicting who will become addicted to opioids in the course of pain treatment.<sup>281</sup>
- IV. Webster wrote, “When physicians agree to perform surgery but then refuse to treat postoperative pain, their fear of prescribing opioids has become exaggerated. The refusal to adequately relieve postsurgical pain is

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<sup>277</sup> Discussed below at Section §C.10.t. and Appendix IV.

<sup>278</sup> ENDO-CHI\_LIT-00538705, at -8713.

<sup>279</sup> *Id.* at -8717.

<sup>280</sup> Discussed above at Section §C.8.r.

<sup>281</sup> Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

unconscionable.”<sup>282</sup> This statement falsely conflates relieving post-surgical pain with prescribing opioids. Non-opioids work just as well or better than opioids in many instances of acute pain. Further, perioperative opioids for acute pain have become a major gateway to persistent opioid use and opioid use disorder.<sup>283</sup>

V. Webster wrote, “As a hallmark of the increasing acceptance of analgesics used to control pain, a 1997 consensus document published by the American Academy of Pain Medicine and the American Pain Society advised all types of clinicians (not just specialists) to consider the use of opioids in selected patients for the management of chronic nonmalignant pain.”<sup>284</sup> The AAPM and APS consensus document was funded by industry, scientifically inaccurate, and ultimately discredited.

C. Dr. Lynn Webster’s own Curriculum Vitae reports that he was on the American Academy of Pain Medicine (AAPM) Board of Directors from 2007 through at least 2016, president-elect/president of the AAPM from February 2012 to March 2014, Director-at-large of the AAPM from 2008-2010, and Treasurer from 2010-2011 (also chairing finance and fundraising committees).<sup>285</sup> Findings from a U.S. Senate Finance Committee investigation of opioid manufacturers’ financial relationships with patient advocacy groups and other entities reported payments by various opioid manufactures to the AAPM during this time 2007-2016 period including \$858,320 from Endo, \$172,525 from Janssen/Johnson & Johnson, \$1,359,715 from Purdue, and \$ 1,022,675 from Teva/Cephalon.<sup>286</sup> Also, Dr. Webster was program chair for AAPM CME programs on opioid prescribing that were funded by opioid manufacturers including Endo, Mallinckrodt and Purdue.<sup>287</sup>

<sup>282</sup> ENDO-CHI\_LIT-00538705, at -8717. *See* discussion of opioid overprescribing after surgery, below, at Section §C.10.q

<sup>283</sup> As discussed below in Section §C.10.q.

<sup>284</sup> *Id.* at -8725.

<sup>285</sup> ENDO-OPIOID\_MDL-03699994, at -9996.

<sup>286</sup> United States Senate Committee on Finance, Findings from the Investigation of Opioid Manufacturers’ Financial Relationships with Patient Advocacy Groups and other Tax-Exempt Entities (December 16, 2020) <https://www.finance.senate.gov/imo/media/doc/2020-12-16%20Finance%20Committee%20Bipartisan%20Opioids%20Report.pdf>. at Appendices A-B

<sup>287</sup> ENDO-OPIOID\_MDL-04066791, at -6797 and -6800.

- D. On one of his CVs, Dr. Webster disclosed that he worked as a consultant for Cephalon and on advisory boards for Alpharma, Cephalon, Purdue and others.<sup>288</sup> On a 2005 Clinical Investigator Financial Disclosure form, Dr. Webster reported that he received a total \$17,200 from Cephalon in 2004 “for speaking.”<sup>289</sup> In 2008, Dr. Webster signed a 3 year consulting agreement with Purdue.<sup>290</sup> Also, in 2011, Cephalon contracted with Dr. Webster to serve as a consultant on Cephalon’s Pain Franchise Medical Scientific Advisory Board, for \$4,500 for 1.5 days work.<sup>291</sup> In 2016, Teva also contracted Dr. Webster to serve as a Medical Expert Consultant for Vantrela ER at \$500 an hour.<sup>292</sup>
- viii. The Pharmaceutical Opioid Industry continues to spend significant amounts of money to promote their products, including payments for “consulting” relationships with influential doctors and educators. An analysis of CMS Open Payment data for non-research payments by companies marketing opioids to teaching hospitals from 2013-2018 found that “[o]verall, there were 444 payments linked to opioid products totaling \$7,023,140 (median value of individual payment \$1348; IQR \$245 to \$20,291)... In addition to payments linked to opioids, we identified 5,168 payments made by 22 companies marketing opioids which were not linked to any opioid or non-opioid product; the total value of these payments was \$120.0 million.”<sup>293</sup> Of the \$7 million linked to specific opioid products, \$3.7 million of that was for “consulting fees”.<sup>294</sup> The products promoted at teaching hospitals include Endo’s Opana, Purdue’s OxyContin, Hysingla, and Butrans, and Janssen’s Nucynta.<sup>295</sup>
- g. Medical School Curricula
- i. In 2003, Purdue entered into an agreement with Harvard Medical School that provided for a significant financial contribution from Purdue to Harvard, as well as a cooperative arrangement between the two entities in developing curriculum and materials for instruction about pain management. In particular, Attachment B to the Agreement

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<sup>288</sup> ENDO-OPIOID\_MDL-00307222, at -7224-7225.

<sup>289</sup> TEVA\_AAMD\_00629997.

<sup>290</sup> PPLP003478494

<sup>291</sup> TEVA\_MDL\_A\_07249903

<sup>292</sup> TEVA\_MDL\_A\_06746958, at -6967.

<sup>293</sup> Anderson TS *et al.* Financial payments to teaching hospitals by companies marketing opioids. *J. General Internal Medicine* (2019), at p. 1.

<sup>294</sup> *Id.* at Table 2.

<sup>295</sup> *Id.* at Table 1.



provides that (i) “Purdue Pharma shall be encouraged to suggest ideas for areas where education in the field of pain is needed, and for curriculum which might meet such needs”; (ii) “Purdue Pharma shall be encouraged to suggest ideas for CME [Continuing Medical Education] courses”; and (iii) with respect to the goals of the educational program, “Purdue Pharma shall be encouraged to make suggestions concerning such courses and materials.”<sup>296</sup>

- ii. In 1999, Purdue Pharma funded the new Pain Research, Education and Policy (PREP) program at Tufts University School of Medicine, contributing more than \$2 million to the venture over the next 10 years.<sup>297</sup> In addition to monetary gifts, a Purdue representative sat on the PREP steering committee, a privilege that included the opportunity to influence the medical school curriculum and encourage preferred research.<sup>298</sup> Purdue gave \$380,000 for Tufts’ Center for the Study of Drug Development (CSDD), which conducted research for pharmaceutical companies, regulators, and policymakers.<sup>299</sup> Purdue also funded the Comprehensive Educational Program (CEP) to host projects in the interest of both Tufts and Purdue.<sup>300</sup>
- iii. David Haddox, a senior executive of and Key Opinion Leader for Purdue (and co-author of the article that inspired the misleading concept of “pseudoaddiction” discussed in more detail at Section §C.4.n) was appointed an adjunct faculty member and regular lecturer in Tufts PREP program until 2018.<sup>301</sup> According to a detailed analysis of Tufts relationship with Purdue, including classes taught by Haddox, the report found that Haddox did not address opioid use disorder in his lectures on opioids and analogized “regulation of opioids to Prohibition.”<sup>302</sup>
- iv. Daniel Carr, Tufts University School of Medicine Professor of Public Health and Community Medicine and vocal advocate for chronic pain treatment with opioids, became director of PREP and testified to the FDA in 2002 as Purdue’s consultant.<sup>303</sup> He defended Purdue’s role in the opioid crisis and was a vocal critic of “opioidphobia” which he

<sup>296</sup> PPLPC021000425373, at Appendix B. The industry also made substantial contributions to the University of Wisconsin - Madison School of Medicine, *see* discussion at §C.4.i. and Appendix II.

<sup>297</sup> Caleb Symons, Austin Clementi, *Report reveals loose conflict-of-interest policies, deference to donors benefitted Purdue Pharma*, The Tufts Daily, Dec. 6, 2019. <https://tuftsdaily.com/news/2019/12/06/sackler-report-reveals-lack-due-diligence-tufts/>, at p. 1.

<sup>298</sup> *Id.* at p. 2.

<sup>299</sup> *Id.*

<sup>300</sup> *Id.*

<sup>301</sup> *Id.*

<sup>302</sup> *Id.* at p. 5.

<sup>303</sup> *Id.* at pp. 2-3.



defined as an irrational fear of prescribing opioids for chronic pain.<sup>304</sup> Richard Sackler, president of Purdue from 1999 to 2003, was a member of Tufts University School of Medicine Board of Advisors for almost 20 years until his resignation in 2017.<sup>305</sup> Carr was editor of a widely circulated, Purdue sponsored continuing education brochure directed at prescribers and pharmacists that included the false and misleading statement, “Barriers to their clinical use for chronic noncancer pain include widely unwarranted fears of addiction (psychological dependence); exaggerated risks of respiratory depression and other side effects; and overcaution regarding tolerance, withdrawal, and diversion. When used at appropriate doses to treat pain in selected patients provided with multidisciplinary followup, opioids are very unlikely to produce iatrogenic addiction.”<sup>306</sup>

- v. A January 2011 email thread describes collaboration between opioid manufacturers, including Endo and Purdue, represented by David Haddox, and the Tufts Health Care Institute (THCI) in development of the “THCI Program on Opioid Risk Management.”<sup>307</sup> The email discussion notes THCI is “interested in looking at how approaches/strategies used by different types of organizations lead to physician behavior change, and to explore how these approaches might be applied to opioid prescribing.”<sup>308</sup>
- vi. Since 1980, Tufts University School of Medicine has accepted approximately \$15 million from Purdue and the Sackler family.<sup>309</sup> By 2019, Tufts Board of Trustees had reconsidered its relationship with Purdue and the Sackler family, removed the Sackler name from all buildings on its Boston Health Sciences Campus, and established a \$3 million endowment to prevent and treat substance use disorders.<sup>310</sup>
- vii. I also personally experienced the influence of the pharmaceutical industry on the curriculum during my own medical education in the 1990s. Our pain curriculum emphasized opioids as a safe and effective first-line treatment for all types of pain, including chronic pain; failed to provide information on the risks of misuse, addiction, dependence, and overdose; provided no information on how to monitor for misuse/addiction or taper patients off of opioids when harms outweighed benefits; and suggested that physicians who refused opioids to patients in pain were lacking in integrity and compassion.

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<sup>304</sup> *Id.* at p. 6.

<sup>305</sup> *Id.* at p. 3.

<sup>306</sup> PDD1501608597 at 8607.

<sup>307</sup> ENDO\_ALAG-00401074.

<sup>308</sup> *Id.* at -1076.

<sup>309</sup> *Id.* at p. 2.

<sup>310</sup> *Id.* at p. 7.

- h. Continuing Medical Education.
  - i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.<sup>311</sup>
  - ii. Drug company-sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.<sup>312</sup>
  - iii. A 2021 study states that "despite being characterized as 'educational', industry-sponsored events are almost always associated with other payments and/or gifts" and "between 2013-2015, 1 in 12 United States physicians (and 1 in 5 primary care physicians) received a payment from an opioid manufacturer, which was most commonly in the form of food or beverages or speakers' fees, suggesting that attendance at industry-sponsored drug dinners or other educational events is widespread."<sup>313</sup>
  - iv. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.<sup>314</sup>
  - v. The use of "Speakers Bureaus" of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy. "From 1996 to 2001, Purdue conducted more than 40 national pain-management and

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<sup>311</sup> Lurie, "Doctors Receive Opioid Training", fn. 272, above, at p. 3.

<sup>312</sup> Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. <http://dx.doi.org/10.1001/jama.283.3.373>, at pp. 373, 377-78.

<sup>313</sup> Grundy Q, *et al.* A comparison of educational events for physicians and nurses in Australia sponsored by opioid manufacturers. *PLOS One*. 2021;16(3):1-18, at p. 3.

<sup>314</sup> Saper, "The Influence of Pharma," fn. 240, above, at p. 2.

speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue's national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns."<sup>315</sup>

- vi. The blurred lines between "education" and "promotion" were also evident at Endo and raised concerns from its clinical affairs staff.
  - A. In August 2007, Linda Kitlinski, a member of Endo's clinical affairs department responsible for pain-related educational grants, raised concerns regarding the inappropriateness of Endo Marketing having the ability to pre-approve or make changes to continuing medical education materials before review by Endo's Promotional Material Review Board ("PMRB"). Kitlinski questioned "why would a CME brochure have to be pre-approved by Marketing? This would be against guidelines"<sup>316</sup> and further noted that it does "seem inappropriate from a CME standpoint" for marketing product manager(s) to pre-approve or make changes to a CME prior to PMRB review.<sup>317</sup>
  - B. An August 6, 2009 email thread between Endo Clinical Affairs Managers further suggests lines were crossed between Endo sales and clinical affairs. In reply to Frank Yuen<sup>318</sup> who expressed concern about Clinical Affairs Managers ("CAMs") going "on record as sharing any of the stated sales objectives"<sup>319</sup> for pain related educational initiatives. Endo's Associate Director of Clinical Development & Education,<sup>320</sup> Vin Torno replied that "We CAMs are on record as owning Endo's objectives to meet its corporate sales goals/numbers."<sup>321</sup> Although agreeing that Clinical Affairs should stay on the "right side of the firewall and engage in appropriate activities to support sales" Torno went on to state

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<sup>315</sup> Van Zee, "The Promotion and Marketing of OxyContin", fn. 101, above, at pp.221-22.

<sup>316</sup> ENDO\_FLAG-01167983, at -7984.

<sup>317</sup> *Id.*, at -7983.

<sup>318</sup> Frank Yuen's title was "Clinical Affairs Manager, Endo Pharma." ENDO\_SF-00108422.

<sup>319</sup> ENDO-OPIOID\_MDL-07485510, at -5511.

<sup>320</sup> Vin Torno's full title was "Associate Director, Clinical Development & Education, Scientific Affairs, Endo Pharma" ENDO\_FLAG-00405575

<sup>321</sup> ENDO-OPIOID\_MDL-07485510, at -5510.

the importance of Clinical Affairs as part of the “crossfunctional initiative,” because “If you’re not sitting at the table, you’ll be on the menu.”<sup>322</sup>

- vii. Endo budgeted more than \$7 million for Promotional Speaker Programs, out of a total annual budget of \$15.8 million dollars, to promote Opana in 2009,<sup>323</sup> describing the importance of their plan through the promotional effort as follows: “Key to OPANA ER’s Growth in 2008 is the Completion of Over 720 Promotional Speaker Programs in the 1<sup>st</sup> Half,”<sup>324</sup> and “Positive ROI for OPANA Promotional Speaker Programs,” showing nearly 200% ROI by 28 weeks.<sup>325</sup> The objective was to “grow OPANA ER market share by 1%” with TRx of 640,000 and net sales of OPANA ER at \$190 million.<sup>326</sup>
- viii. Endo also sponsored a series of Continuing Education “opioid dinner dialogues” in 2008 with the National Initiative on Pain Control (NIPC) titled “Chronic Opioid Therapy: Understanding Risk While Maximizing Analgesia.”<sup>327</sup> The presentation states that the NIPC and the CE program were supported by a grant from Endo and included multiple case studies recommending opioids for the treatment of chronic low back pain<sup>328</sup> despite that “the current literature does not support that opioids are more effective than other groups of analgesics for LBP [low back pain] such as anti-inflammatories or antidepressants.”<sup>329</sup> Program speakers included KOLs Lynn Webster, David Fishbain, Perry Fine, and Steven Stanos, and addressed audiences comprised of doctors, dentists, nurse practitioners and pharmacists.<sup>330</sup> These “opioid dinner dialogues” were held nationwide.<sup>331</sup>
- ix. By November 2009, Linda Kitlinski, the Endo employee responsible for pain-related educational grants mentioned above, had become “increasingly concerned” the “there is among Endo’s senior leadership (VP level and up) ever-increasing pressure to link independent

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<sup>322</sup> *Id.*

<sup>323</sup> ENDO-CHI\_LIT-00023217, at \*81 (produced natively).

<sup>324</sup> *Id.* at \*19.

<sup>325</sup> *Id.* at \*20.

<sup>326</sup> *Id.* at \*33.

<sup>327</sup> ENDO\_FLAG-00455141

<sup>328</sup> ENDO\_FLAG-00306923 (produced natively), at \* 3 and \*26-\*109.

<sup>329</sup> Chaparro LE, *et al.* Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD004959.pub4 at p. 2. The Chaparro study is discussed in greater detail below at §C.7.d.

<sup>330</sup> ENDO\_FLAG-00421543; ENDO\_FLAG-00421545.

<sup>331</sup> ENDO\_FLAG-00421545

education directly to Endo's Commercial business/branded products."<sup>332</sup> In an email titled "Note to LK's Personal File," and sent to her husband because of fears of potential adverse consequences due to her opposition to Endo's policies, Kitlinski described "increasing concerns over the pressures to 'cross the line'" to engage in promotional activities more appropriate for sales or management market team members.<sup>333</sup> Kitlinski's concerns included the reorganization of 6 members of the Clinical Affairs team to a separate Health Outcomes and Pharmacoeconomics (HOPE) department "charged with working closely with the Account Executives and Regional Sales Directors, and focusing their efforts on 'payors'"<sup>334</sup> and a request from the COO and VP of Scientific Affairs to send a list of proposed educational grants to the VPs of the Commercial Business unit.<sup>335</sup> Kitlinski's direct manager warned her to stop "playing policeman"<sup>336</sup> on compliance issues and Kitlinski feared being "'let go' in what might appear to be a 'business-related head count reduction' but which would actually be related to my 'conservative' interpretation of what is/is not appropriate to Endo's education grant making practices."<sup>337</sup>

- x. Endo continued to sponsor nationwide opioid "dinner dialogues" in 2012, titled "Responsible Opioid Prescribing in the Era of REMS."<sup>338</sup> The presentation for the event referenced the 2009 clinical guidelines for the use of opioids in chronic noncancer pain at least 28 times<sup>339</sup> while omitting that the study's evidence regarding chronic opioid therapy was of "low quality," meaning that it was "insufficient to assess effects on health outcomes."<sup>340</sup> More than half of the study's authors (13/21) had conflicts of interest arising from payments by opioid manufacturers, including Endo.<sup>341</sup>
- xi. Teva/Cephalon Pharmaceutical's "2005 ACTIQ Marketing Plan" tactical summary of sales strategies clearly delineate how they planned to use misleading marketing messages in the form of "continuing medical education" to promote their products, including their branded-fentanyl product "Actiq." Teva/Cephalon's strategy focused on persuading doctors of the need for ACTIQ as a supplement to chronic opioid therapy, to treat so-called "Breakthrough Pain," (BTP) when in

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<sup>332</sup> ENDO\_SF-00588257.

<sup>333</sup> *Id.*

<sup>334</sup> *Id.* at -8258.

<sup>335</sup> *Id.* at -8259.

<sup>336</sup> *Id.* at -8257.

<sup>337</sup> *Id.* at -8259.

<sup>338</sup> EPI002487105; EPI002487106

<sup>339</sup> EPI002487106

<sup>340</sup> Chou R, *et al.* Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*. 2009;10(2):113-130, at p. 130.e5. The 2009 Clinical Guidelines are discussed in detail at §C.7.d.

<sup>341</sup> *Id.*, at Appendix 1.

fact such patients likely sought greater doses of opioids because they had experienced “tolerance,” that is, they needed greater amounts of opioids to get the same degree of pain relief. This practice led to patients being on higher cumulative doses of opioids, increasing their risk of addiction and death. See excerpted quotes below which describe Teva/Cephalon’s CME plan:

- A. “ACTIQ marketing strategies will be executed through a variety of tactical initiatives that convey ACTIQ key messages and differentiate ACTIQ from its competitors based on its primary patient benefit, rapid onset of analgesia and pain relief.... Both promotional and continuing medical education programs will be implemented in 2005 and will continue to comprise a critical component of the tactical plan. New in 2005 is *Emerging Solutions in Pain (ESP)* which is an initiative developed by physicians for physicians, pharmacists and other healthcare professionals, to address some of the most critical issues in pain management today.”<sup>342</sup>
- B. “Continuing Medical Education CME played a vital role in the education of physicians, nurses and pharmacists in 2004 regarding chronic cancer pain and non-cancer pain and Abuse, Addiction and Diversion. The major CME initiatives in 2004 included a CME on-demand teleconference, local and regional CME symposia (CEP Lectures), a tri-mesterly newsletter entitled *Emerging Solutions in Pain*, a repository website by the same name *EmergingSolutionsinPain.com*, sponsorship of the *Pharmacologic Management of Pain Resource Center* on Medscape and the sponsorship of the Breakthrough Cancer Pain category on pain.com, the most popular pain website on the internet. Additional CME initiatives included a CME insert in *CME-TODAY* for Primary Care Physicians and CME Symposia at the annual congresses for AAPM, AAPM&R and the Northeast PRI-MED.”<sup>343</sup>
- C. “The local and regional CME Symposia represented one of the most significant educational efforts in the area of pain management in 2004. These symposia allowed for the scientific exchange of extensive information on diagnosis, assessment and management of various pain related issues. Approximately 214 of these programs are expected to be completed by year end.”<sup>344</sup>

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<sup>342</sup> TEVA\_CAOC\_00759630 at -9634.

<sup>343</sup> *Id.* at -9664.

<sup>344</sup> *Id.*

- D. “The tri-annual newsletter, Emerging Solutions in Pain, currently has a circulation of over 11,000 clinicians (8,000+ physicians and 2000+ nurses). The newsletter allows for communication of information on diagnosis and management of various pain types, in two distinct media: written and CD-ROM. The accompanying website serves as a repository for all CME programs created.”<sup>345</sup>
    - E. The newsletter, website, and above-described CMEs were all used to spread the false and misleading messages documented in this report.
  - xii. I have personally experienced this strategy of marketing messages misrepresented as CME. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.
  - i. Seeding the Medical Literature
    - i. The Pharmaceutical Opioid Industry seeded the very foundation of evidence-based medicine, the peer-reviewed medical literature, by promoting studies that supported use of opioids for chronic pain based on misleading evidence. A common practice was the use of studies showing *short term* benefit of opioids (12 weeks or less) in patients with chronic pain (pain every day for 3 months or more); which is different than studies showing *long-term* benefit of opioids in patients with chronic pain, a subtle but crucial distinction. Endo’s 2008 campaign to promote Opana for chronic pain funded and tracked 18 abstracts and presentations for 2008,<sup>346</sup> including the following 12-week studies promoting opioids for chronic pain:<sup>347</sup>

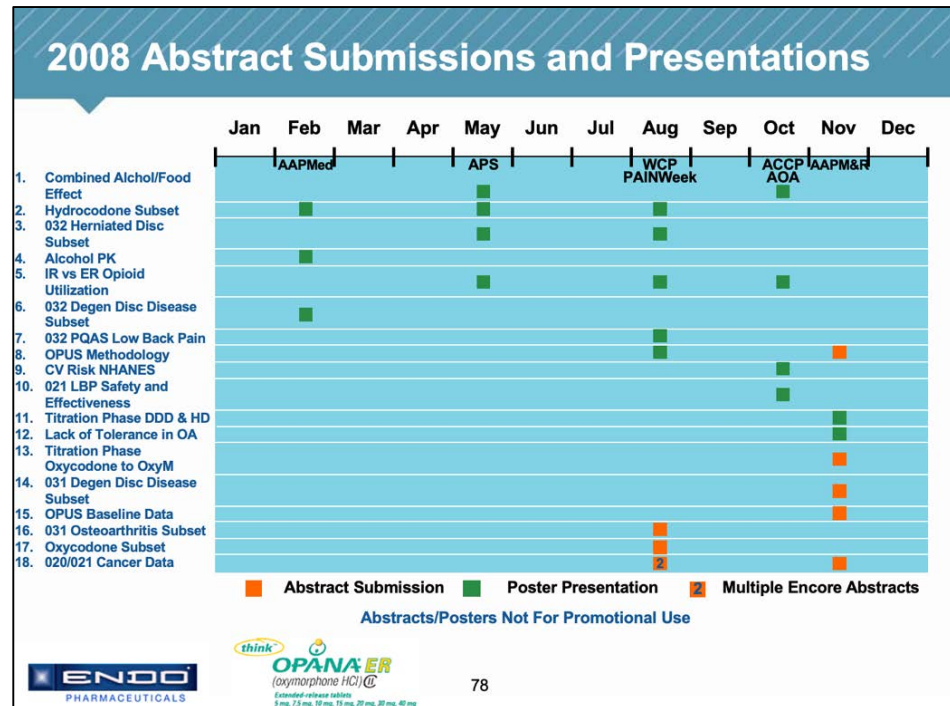
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<sup>345</sup> *Id.*

<sup>346</sup> Nine of the eighteen studies were co-authored by Endo employees (Harry Ahdieh, R A. Puenpatom).

<sup>347</sup> ENDO-CHI\_LIT-00023217, at \*78 (produced natively). See ENDO-OPIOID\_MDL-06656285 (Opana ER tab) Endo-supported abstracts were submitted and/or presented at conventions or conferences for the American Academy of Pain Medicine, American Pain Society, International Association for the Study of Pain – World Congress on Pain, PAINWeek, American Osteopathic Association, American College of Clinical Pharmacy, and the American Academy of Physical Medicine & Rehabilitation. ENDO-OPIOID\_MDL-06825188 at 191-192.





- A. For example, a 12-week study reported that patients with “chronic low back pain” experienced “effective and durable analgesia” with Opana ER. The Hale study is misleading in that it implies Opana ER is beneficial for chronic pain, based on a study of short-term use. It also promotes safety of Opana ER in a misleading manner by reporting no serious adverse effects, without disclosing that the risks of the most serious adverse effects of OUD and mortality increase with dose and duration of exposure, and that the dose is often increased over time due to the phenomenon of tolerance, that is, a greater dose is required to achieve the same degree of pain relief.<sup>348</sup> By 2009, the Hale study was being provided to Endo sales reps as a tool to help promote Opana ER for lower back pain patients.<sup>349</sup>
- B. A study by Gammaitoni *et al* was titled “Opana ER improves pain quality measures in opioid-experienced patients with chronic low back pain,” implying that it worked for chronic

<sup>348</sup> Hale, Martin & Ma, Tasneem & Ahdieh, H. & Kerwin, R.. Efficacy of oxymorphone extended release in opioid-experienced patients with chronic low back pain due to a herniated disc: Subgroup analysis of a randomized, double-blind, placebo-controlled trial. *Journal of Pain*. 2008;9: 40-40. 10.1016/j.jpain.2008.01.180.

<sup>349</sup> ENDO ALAG-00413097.

pain. Not true. The study itself was only 12 weeks long and inappropriately used to promote Opana for chronic pain.<sup>350</sup>

- C. Podolsky *et al* did a randomized clinical trial of the safety and efficacy of oxymorphone extended release for degenerative disc disease in opioid-naïve patients. This abstract begins with the scientifically invalid assertion, “It was previously demonstrated that oxymorphone extended release (OPANA ER) is safe and effective for treating chronic low back pain in opioid-naïve patients.” The abstract then made similar claims that Opana ER is “efficacious” for patients with chronic degenerative disc disease, based on another 12 week study. Notably, on the same page of the same set of conference abstracts, authors sponsored by Johnson and Johnson made essentially identical, misleading claims of efficacy of its tapentadol opioid product for chronic back pain, attesting to further evidence of the widespread use of inadequate short-term studies to claim long-term safety and efficacy.<sup>351</sup>
- ii. Endo also “generously sponsored” a Supplement to the April 2009 edition of Pain Medicine, entitled, “Oxymorphone,” featuring Guest Editor David Fishbain, MD.<sup>352</sup> Fishbain’s Introduction failed to disclose that he had served on a Speaker’s Bureau for Endo,<sup>353</sup> and that he had been a litigation expert for Purdue on multiple occasions.<sup>354</sup> Fishbain described the purpose of the Supplement to provide the “busy clinician” with one volume to get an “overall impression of the status of the research, rather than searching among various journals and poster abstracts.”<sup>355</sup> One of the articles in the Supplement was authored by Joseph Pergolizzi, “a speaker and consultant for Endo Pharmaceuticals,”<sup>356</sup> and other included materials cited to Endo’s own research, such as the articles by Hale and Katz, which were misleadingly used by Endo to claim efficacy for long-term treatment of chronic pain based on short-term studies.<sup>357</sup> “Busy clinicians” who read the Endo-sponsored Supplement would have been falsely reassured by the assertion, “Recent reviews of oxymorphone have concluded that as

<sup>350</sup> Gammaitoni A, Gould E, Ahdieh H, *et al.* Opana ER improves pain quality measures in opioid-experienced patients with chronic low back pain. *Journal of Pain*. 2007;8(4):S440

<sup>351</sup> Podolsky G, Ahdieh H, Ma T, Gould E. Randomized clinical trial of the safety and efficacy of oxymorphone extended release for degenerative disc disease in opioid-naïve patients. *Journal of Pain*. 2009.

<sup>352</sup> END00006991, at 6998-6999.

<sup>353</sup> *Id.* See ENDO\_FLAG-00421543; ENDO\_FLAG-00421545.

<sup>354</sup> Graves v. Purdue Pharma Ltd, *et al.* Rule 26(a)(2) Disclosure of David A. Fishbain, MD, Civil Action 2:07cv107-MPM-SAA (USDC NMS)

<sup>355</sup> END00006991, at -6998.

<sup>356</sup> *Id.* at -7043.

<sup>357</sup> *Id.* at -7007, -7009, -7044

an analgesic, its effectiveness, safety, tolerability, and documented viability as an analgesic over year-long studies may make it a valuable addition to the pain management armamentarium for cancer- and noncancer related disease states.”<sup>358</sup> The sources cited in the 2009 Endo Supplement for this misleading statement included articles by Joseph Gimbel and Alan Matsumoto, both of whom had previously authored articles “Supported by Endo Pharmaceuticals Inc.”<sup>359</sup>

- j. Clinical Decision Support Tools
  - i. Clinical decision support (“CDS”) tools help doctors know when and how to provide certain types of treatments. In a world of voluminous information, these tools distill complex data into simple-to-read flowcharts and algorithms to guide prescribers. They come in many different forms, from reminders on pocket cards, to infographics on wall posters, to prompts and alerts in the electronic medical record system.<sup>360</sup> When based on scientific evidence these tools can be helpful. When not, they can mislead large numbers of doctors.
  - ii. For example, in January 2020, Practice Fusion, Inc., a provider of electronic health records (EHRs) including CDS tools embedded within the EHRs, “admitted to conspiring with an opioid manufacturer to create a pain alert tool to encourage physicians to prescribe more extended release opioids,” and agreed to pay \$145 million to resolve criminal and civil allegations that it accepted ‘kickbacks’ in exchange for creating and implementing a CDS that promoted such prescribing.<sup>361</sup>
  - iii. According to an article in *JAMA*, “The resulting alerts promoted opioid prescribing that deviated from accepted medical standards by suggesting extended-release opioids as a treatment option for patients

<sup>358</sup> *Id.* at -7014.

<sup>359</sup> See END00006991 at -7016, citing Gimbel JS. Oxymorphone: A mature molecule with new life. *Drugs Today* 2008;44(10):767-82., an article which does not disclose a link to Endo; however, see also, Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: Results of a randomized, double-blind, placebo- and active-controlled Phase III study. *The Journal of Pain*. 2005;6(1):21-28, which was supported by Endo. See also, Matsumoto, A. K., Babul, N., & Ahdieh, H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain Medicine*, 2005;6(5), 357–366, this study was also supported by Endo.

<sup>360</sup> U.S. Department of Health and Human Services. *Clinical Decision Support*. (April 10, 2018). <https://www.healthit.gov/topic/safety/clinical-decision-support>.

<sup>361</sup> Taitsman JK, et al. Commercial Influences on Electronic Health Records and Adverse Effects on Clinical Decision Making. *JAMA Intern Med*. 2020;10.1001/jamainternmed.2020.1318. doi:10.1001/jamainternmed.2020.1318, at p. E1. According to recent reports, Purdue Pharma is the previously unnamed “opioid manufacturer” that conspired with Practice Fusion, and Purdue Pharma has pleaded guilty to that conspiracy. <https://www.nytimes.com/2020/10/21/health/purdue-opioids-criminal-charges.html>

with less than severe pain, even if nonopioid or immediate-release opioid alternatives could have adequately controlled the pain. Physicians who received these pain alerts prescribed extended-release opioids at a higher rate than those who did not.”<sup>362</sup> A statement by the United States Department of Justice stated, “In marketing the ‘pain’ CDS alert, Practice Fusion touted that it would result in a favorable return on investment for the opioid company based on doctors prescribing more opioids.”<sup>363</sup> Such prescribing exposed patients to increased risks of harms caused by prescription opioids.

- iv. Other examples of clinical decision support tools include items like the “Pain Evaluator” pictured below, described by Endo as a “Pain Assessment tool which will help the HCP [health care provider] understand the patients [sic] pain, not limited to a number on the scale but a clearly [sic] understanding of what they can do because of pain.”<sup>364</sup> The Pain Evaluator consists of a series of happy to sad faces, with the happiest face representing “no hurt” and the saddest face representing “hurts worst.” Beyond its grammatical flaws, the Pain Evaluator has never been shown to improve pain outcomes and does not add to understanding patients’ pain. Rather, such tools have been shown to increase opioid prescribing.<sup>365</sup>

**Educational Access Tool**

Optimize targeting for more efficient deployment of resources on highest potential targets

- Objective:**
  - To support the sales efforts by providing them with additional educational tools
- Description:**
  - Pain Assessment tool which will help the HCP understand the patients pain, not limited to a number on the scale but a clearly understanding of what they can do because of pain.
- Audience:**
  - Call Plan Healthcare Prescribers
- Timing:**
  - Q1
- Investment:**
  - \$180,000

**How to use the Pain Evaluator**

Below the slider from left to right, increasing your overall pain level. Need select 'yes' or 'no' in response to the suggested tasks. If not applicable, please choose 'yes'.

**What is your overall pain level? \***

Are you capable of performing these tasks?

	Work	Home	Misc.
Walking	Yes	Yes	Yes
Standing	Yes	Yes	Yes
Sitting	Yes	Yes	Yes
Lying down	Yes	Yes	Yes
Driving	Yes	Yes	Yes
Working	Yes	Yes	Yes
Walking	Yes	Yes	Yes
Standing	Yes	Yes	Yes
Sitting	Yes	Yes	Yes
Lying down	Yes	Yes	Yes
Driving	Yes	Yes	Yes
Working	Yes	Yes	Yes

**ENDO PHARMACEUTICALS** **OPANA ER** **Pain Evaluator**

<sup>362</sup> *Id.*

<sup>363</sup> US Department of Justice. *Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil Investigations* (January 27, 2020). <https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0>

<sup>364</sup> ENDO-CHI\_LIT-00023217, at \*62 (produced natively).

<sup>365</sup> Lembke, “Drug Dealer MD”, fn. 3, above, at p. 66, citing to Vila Jr. H, *et al.* The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: Is patient safety compromised by treatment based solely on numerical pain ratings? *Anesth Analg.* 2005;101:474-80, and Frasco PE, *et al.* The impact of the Joint Commission for Accreditation of Healthcare Organizations pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg.* 2005;10:162-8.

**How to use the Pain Evaluator**  
Move the slider from left to right to select your overall pain level.  
Next select "yes" or "no" in response to the suggested tasks.  
If not applicable, please choose "yes".

**What is your overall pain level ? \***

0 1 2 3 4 5 6 7 8 9 10

NO HURT HURTS LITTLE BIT HURTS LITTLE MORE HURTS EVEN MORE HURTS WHOLE LOT HURTS WORST

**Are you capable of performing these tasks?**

Category	Task	Response
Work	typing	YES
	using a mouse	YES
	holding a phone	YES
	writing	NO
	attending meetings	YES
	turning pages	YES
	lifting weight	YES
	sitting at a desk	YES
	reading a book	NO
	Home	doing laundry
playing with kids		YES
doing dishes		NO
cleaning house		YES
preparing a meal		NO
mowing the lawn		YES
grocery shopping		NO
taking a bath		YES
blow drying hair		YES
Misc.		driving
	hiking	YES
	riding a bike	YES
	sleeping thru night	YES
	exercising	NO
	walking a dog	YES
	walking up stairs	NO
	gardening	YES
	other recreational activities	YES

**Pain Evaluator**

- k. Professional Medical Societies and Patient Advocacy Groups
- i. According to Janssen's response to a May 2012 US Senate Finance Committee request, between 1997-2012 Janssen and its parent, Johnson & Johnson, made payments totaling more than \$4 million dollars to professional societies such as the American Pain Society, the American Academy of Pain Medicine, and the Joint Commission Resources, to promote pain treatment practice guidelines that advocated unwarranted expanded use of opioids.<sup>366</sup> From 2012-2017, Janssen continued payments and close coordination with these groups, providing almost a half a million dollars in funding. Janssen also acknowledged making payments via a third party to patient advocacy groups (see below).<sup>367</sup>
  - ii. The US Senate Finance Committee subsequently issued findings from its investigation into opioid manufacturers' financial relationships with professional medical societies and patient advocacy groups on December 16, 2020.<sup>368</sup> According to the Finance Committee's report, "To date, the Committee has identified approximately \$65 million in payments that opioid manufacturers and related companies have made to tax-exempt entities, which suggests that manufacturers view these organizations as helpful extensions of their sales and marketing efforts."<sup>369</sup>
  - iii. The Senate findings show that between 1997 and 2012, the American Pain Society, the American Academy of Pain Medicine, and the American Pain Foundation, among others, received significant funding

<sup>366</sup> JAN-MS-00000001.

<sup>367</sup> HSGAC Report, "Fueling an Epidemic", fn. 260, above, at pp. 1, 17.

<sup>368</sup> United States Senate Committee on Finance, Findings from the Investigation of Opioid Manufacturers' Financial Relationships with Patient Advocacy Groups and other Tax-Exempt Entities (December 16, 2020) <https://www.finance.senate.gov/imo/media/doc/2020-12-16%20Finance%20Committee%20Bipartisan%20Opioids%20Report.pdf>.

<sup>369</sup> *Id.* at p. 2.

from Endo (\$13.5 million), Johnson & Johnson (\$4.0 million), and Purdue (\$18.7 million).<sup>370</sup> The American Pain Society, for example, received more than \$3.3 million in funding from 2012 through 2017 from more than a dozen opioid manufacturers, including Endo, Janssen, Mallinckrodt, Purdue and Teva.<sup>371</sup> In 2012, a separate Senate committee report stated that these manufacturer-supported professional medical societies and patient advocacy groups “have amplified or issued messages that reinforce industry efforts to promote opioid prescription and use, including guidelines and policies minimizing the risk of addiction and promoting opioids for chronic pain.”<sup>372</sup>

- iv. While the Senate Finance Committee investigation is on-going, the “initial review has revealed troubling instances in which patient advocacy groups, and other tax-exempt organizations, their officers, and their board members have engaged in initiatives that appear to echo and amplify messages to increase use of opioid manufacturers’ drugs, including abuse-deterrent opioids that have not been proven to be any less addictive than other types opioids.[sic]”<sup>373</sup>
- v. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Pharmaceutical Opioid Industry, which he referred to as “narcopharma.”<sup>374</sup>
- vi. Consistent with and supportive of my personal experience, Dr. Saper testified that “the educational programs of AAPM [American Academy of Pain Medicine] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.”<sup>375</sup>
- vii. Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were “inappropriate”,<sup>376</sup> and I agree.

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<sup>370</sup> *Id.* at Appendix A.

<sup>371</sup> *Id.* at Appendix B.

<sup>372</sup> HSGAC Report, “Fueling an Epidemic”, fn. 260, above, at p. 12.

<sup>373</sup> Senate Finance Committee, “Findings”, fn. 368, above, at p. 17.

<sup>374</sup> Saper, “The Influence of Pharma,” fn. 240, above, at p. 5.

<sup>375</sup> Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.

<sup>376</sup> *Id.* at 93:15-19.



- viii. Dr. Saper further stated that “APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients.”<sup>377</sup>
- ix. In 2009, Janssen partnered with the American Geriatrics Society and American Academy of Pain Medicine to create a 2009 patient education guide entitled, “Finding Relief: Pain Management for Older Adults.”<sup>378</sup> In 2010, Janssen paid the American Geriatrics Society more than \$158,209 for “educational grants.”<sup>379</sup>
- x. The “Finding Relief” patients’ guide included the claims shown below.<sup>380</sup> These claims were false and misleading in that addiction to prescription opioids is common, not rare, and chronic use does not confer substantial benefit, as discussed later in this Report.

### Opioid myths

**Myth:** Opioid medications are always addictive.

**Fact:** Many studies show that opioids are *rarely* addictive when used properly for the management of chronic pain.

**Myth:** Opioids make it harder to function normally.

**Fact:** When used correctly for appropriate conditions, opioids may make it *easier* for people to live normally.

**Myth:** Opioid doses have to get bigger over time because the body gets used to them.

**Fact:** Unless the underlying cause of your pain gets worse (such as with cancer or arthritis), you will probably remain on the same dose or need only small increases over time.

<sup>377</sup> *Id.* at 115:24-116:6.

<sup>378</sup> HSGAC Report, “Fueling an Epidemic”, fn.260, above, at p. 13.

<sup>379</sup> JAN-MS-00000001 at -0007.

<sup>380</sup> JAN-MS-00000306 at -0315; *see also* JAN00000306.



- xi. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with “leaders of APS, APF [American Pain Foundation] and other pain societies.” Dr. Sackler stated, “Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement.”<sup>381</sup>
  - xii. The Pharmaceutical Opioid Industry targeted more than just physician-membership professional medical societies. For example, nursing societies were also prominently featured as part of their marketing campaign. The Endo “2009 OPANA Brand Strategic Plan” indicates that it would increase “OPANA ER brand awareness at venues where Specialty HCP [health care providers] attend” including the “American Academy of Pain Medicine, American Conference on Pain Medicine, Oncology Nurses Society, American Pain Society, American Society for Pain management [sic] Nursing, American Society of Anesthesiologist [sic], American College of Rheumatology.”<sup>382</sup> As noted in my article referenced at Section §C.3.c, above, nurse practitioners are among the highest opioid prescribing health care professionals, thus targeting such professionals would be expected to increase sales.
- 1. The Federation of State Medical Boards (FSMB)
    - i. FSMB is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor’s license to practice medicine.
    - ii. In 1998, the FSMB released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the FSMB urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards and the lawsuit that usually followed, if they denied a patient opioid painkillers.

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<sup>381</sup> PPLPC045000004928 at 4929

<sup>382</sup> ENDO-CHI\_LIT-00023217, at \*51 (produced natively)

- iii. Between 2007 and 2012, the FSMB received approximately \$1.3 million in funding from Purdue, Johnson & Johnson and Endo.<sup>383</sup>
- iv. In 2007, the FSMB published a book promoting the use of opioid painkillers. This book was sponsored by a “consortium” that included Abbott Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, and the University of Wisconsin Pain and Policy Study Group (“PPSG”).<sup>384</sup> (See Appendix II.)
- v. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board’s Model Guidelines on the Use of Controlled Substances for Pain Management,<sup>385</sup> now entitled Model Policy for the Use of Controlled Substances for Pain Management.<sup>386</sup>
- vi. The American Pain Society, funded and influenced by the Pharmaceutical Opioid Industry, supported PPSG professors David Joranson and June Dahl to “visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain.”<sup>387</sup>
- vii. Drs. Joranson and Dahl, as part of their state to state campaign, designated each state with a letter grade based on their evaluation of state policies that “enhance” or “impede” opioid prescribing.<sup>388</sup> The PPSG had created a hierarchy of letter grades to assess the ‘improvement’ or lack of improvement in making opioids easier to prescribe with fewer penalties to prescribing physicians.<sup>389</sup> The highest grade, from the PPSG’s standpoint, was an “A.” A grade of “C” meant

<sup>383</sup> Senate Finance Committee, “Findings”, fn. 368, above, at pp. 9-10. The Findings note that the FSMB “appears to have changed its policy shortly after the [Senate Finance] Committee’s 2012 inquiry” and no longer accepts grants or funding from pharmaceutical companies.

<sup>384</sup> Fishman, S.(ed.), “Responsible Opioid Prescribing: A Physician’s Guide” (Federation of State Medical Boards, Waterford Life Sciences, 2007). The 2020 US Senate Finance Committee findings note that these types of “industry-developed materials and talking points frequently downplayed or distracted from the addictive nature of prescription opioids” and “these efforts directly influenced the medical community, causing them to widely believe that there was a low risk for addiction among patients with chronic pain – a false narrative promoted by opioid manufacturers to increase use of their opioid products”, fn. 368, above, at p. 8.

<sup>385</sup> WIS\_PPSG\_008292.

<sup>386</sup> Federation of State Medical Board’s Model Guidelines on the Use of Controlled Substances for Pain Management (2004), [http://web.archive.org/web/20050612075051/http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004\\_model\\_pain\\_policy.asp](http://web.archive.org/web/20050612075051/http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp)

<sup>387</sup> Saper, “The Influence of Pharma,” fn. 240, above, at p. 9.

<sup>388</sup> PPLPC036000002758, at -2778

<sup>389</sup> PPLPC017000046138, at -6154

that PPSG considered a particular state to have policies that “impede pain management” and opioid prescribing.

- viii. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt pain laws that encouraged opioid prescribing by shielding physicians from liability, and by making it difficult to refuse to prescribe opioids to patients who request them. Although the statutes may have initially been intended for cancer, acute and end-of-life pain, the statutes do not necessarily include any such limitations. Intractable Pain Laws in various states strengthened physicians’ ability to prescribe opioids and also protected physicians from disciplinary action if the drugs were prescribed in compliance with the terms of the law. It also made it difficult for prescribers to decline to prescribe an opioid when patients demanded them. Under the terms of the law, a prescriber who refused to prescribe opioids to a particular patient was required to refer that patient to another physician who would prescribe opioids.<sup>390</sup>
- ix. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report. Those documents show substantial contributions by several opioid manufacturers, including Janssen, Endo, Ortho-McNeil (an affiliate of Johnson and Johnson), Alpharma,<sup>391</sup> and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).
- x. J&J and Janssen worked with the Robert Wood Johnson Foundation (“RWJF”), which paid \$5,926,294.00 in grants to the University of Wisconsin-Madison School of Medicine, the eventual home of the PPSG between 1997 and 2004.<sup>392</sup> Dr. Richard Payne, co-chair of the National Pain Education Council (NPEC) with Russell Portenoy, was

<sup>390</sup> *Id.*

<sup>391</sup> Actavis (now Allergan) acquired Kadian from Alpharma in 2008; see Press Release, Actavis, Actavis Acquires Kadian; Extends Specialty Drug Portfolio in U.S., (Dec. 30, 2008), <https://www.businesswire.com/news/home/20081230005227/en/Actavis-Acquires-Kadian-Extends-Specialty-Drug-Portfolio>.

<sup>392</sup> MDL\_RWJF\_0000001: Grant ID 032037 for \$1,601,991; MDL\_RWJF\_0000003: Grant ID 036509 for \$998,000; MDL\_RWJF\_0000004: Grant ID 036547 for \$998,865; MDL\_RWJF\_0000005: Grant ID 037589 for \$1,408,628; MDL\_RWJF\_0000009: Grant ID 043412 for \$200,450; MDL\_RWJF\_0000010: Grant ID 043940 for \$421,800; MDL\_RWJF\_0000012: Grant ID 048204 for \$183,680; MDL\_RWJF\_0000013: Grant ID 051813 for \$112,880.

on the Janssen and RWJF medical advisory boards during overlapping periods.<sup>393</sup> NPEC was a Janssen-funded patient advocacy group which Janssen launched in support of the Duragesic tactical plan.<sup>394</sup> RWJF also funded the creation and dissemination of the Model State Guidelines through the Federation of State Medical Boards and its collaboration with PPSG, and provided funding to The Joint Commission as well.<sup>395</sup>

- xi. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing by claiming that the ‘failure’ to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like the FSMB. In their promotional material and “Train the Trainer” course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to legal sanctions. (*See* Appendix I for more detail)
- xii. I remember how the fear of “undertreating pain” permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board and lawsuits that could follow if they denied a patient’s request for opioids.
- m. The Joint Commission
  - i. The Joint Commission is a United States-based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. It went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to “The Joint Commission.” Its positioning statement is “Helping Health Care Organizations Help Patients.”<sup>396</sup>
  - ii. In response to an inquiry from the U.S. Senate Finance Committee, a 2012 letter from The Joint Commission stated that The Joint Commission had received funding from Purdue over a 4-year period from 1999-2002, “for several activities, primarily involving knowledge transfer related to The Joint Commission’s pain management standards,

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<sup>393</sup> JAN-MS-00402671.

<sup>394</sup> JAN-MS-00306713.

<sup>395</sup> PDD1706042217.

<sup>396</sup> The Joint Commission, <http://www.jointcommission.org/>.

although Purdue also funded an effort on metrics development. Purdue's support facilitated the efficient, effective and widespread dissemination of the new pain management standards that were developed by The Joint Commission with modest support from the University of Wisconsin (and no support from Purdue)."<sup>397</sup> The 2012 Joint Commission letter also states that support for its "pain management activities" was provided by Purdue, Endo Pharmaceuticals, Ortho-McNeill, The National Pharmaceutical Council, Pfizer, and Abbott Labs.<sup>398</sup> An attachment to the 2012 letter disclosed a total of \$3,911,942 in "payments or transfers received [by the Joint Commission] from all organizations that develop, manufacture, produce, market, or promote the use of opioid-based drugs."<sup>399</sup>

- iii. According to the US Senate Finance Committee Findings of December 16, 2020, The Joint Commission received over \$2.7 million in funding from Defendants Endo, Johnson & Johnson, and Purdue between 2000-2012.<sup>400</sup>
- iv. Having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also contingent on Joint Commission accreditation. That accreditation is obtained through periodic surveys.
- v. In 2001, The Joint Commission declared pain the "fifth vital sign," alongside heart rate, temperature, respiratory rate, and blood pressure, and promoted the use of the Visual Analog Scale (VAS), a series of happy or sad faces supposedly corresponding to pain levels from 0 (no pain) to 10 (the most extreme pain),<sup>401</sup> exemplified by Endo's Pain Evaluator. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: "Some

<sup>397</sup> Letter from The Joint Commission to Senators Baucus and Grassley, June 29, 2012, at p. 3. [https://www.finance.senate.gov/imo/media/doc/35.%20Joint%20Commission%20Letter%20to%20Sens%20Baucus%20and%20Grassley%20\\_June.29.2012.pdf](https://www.finance.senate.gov/imo/media/doc/35.%20Joint%20Commission%20Letter%20to%20Sens%20Baucus%20and%20Grassley%20_June.29.2012.pdf). The 2012 Joint Commission letter does not state that the University of Wisconsin itself was funded by Purdue, through the grants to its Pain and Policy Study Group.

<sup>398</sup> *Id.*

<sup>399</sup> *Id.* at p. 2 and Attachment A at TJC\_MDL\_000000001.

<sup>400</sup> Senate Finance Committee, "Findings", fn. 368, above, at Appendix A. The Senate Findings show that from 2000 through 2012, The Joint Commission received \$75,000 in funding from Endo, \$515,244 from Johnson & Johnson and more than \$2 million from Purdue Pharma.

<sup>401</sup> Lembke, "Drug Dealer MD", fn. 3, above, at p. 66.

clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death.... This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control.”<sup>402</sup> Per the GAO 2003 report, “During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO’s pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO’s pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO’s Web site. Purdue’s participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin.”<sup>403</sup>

- vi. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler’s assertion that more articles were needed “to help counteract the negative articles in the national media.” Hogen’s email, regarding press coverage of JCAHO pain guidelines, stated, “With respect to generating more articles about pain guidelines, we ‘loaned’ JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant (\$75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea.” This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry’s hidden role.<sup>404</sup>
- vii. As noted above, J&J and Janssen worked with the RWJF to support the Wisconsin PPSG. These entities also worked together to provide funding to The Joint Commission (JCAHO).
- viii. As in the case of Defendant-supported KOL’s, professional medical societies, and patient advocacy groups, the JCAHO and PPSG (financially supported by Janssen and RWJF) were instrumental in

<sup>402</sup> Catan T, Perez E., “A Pain Drug Champion Has Second Thoughts”. *The Wall Street Journal*. December 2012, at p.4.

<sup>403</sup> GAO. Prescription OxyContin Abuse and Diversion and Efforts to Address the Problem. *J Pain Palliat Care Pharmacother*. 2003;18(3):109-113. doi:10.1300/J354v18n03\_12, at p.23.

<sup>404</sup> PDD8801183361 at 3363.



creating new pain treatment standards that promoted increased opioid use as well as opioid-friendly prescribing guidelines in the early 2000s.

- n. Examples of Misrepresentations: “Pseudoaddiction” and “Breakthrough Pain”
  - i. The Pharmaceutical Opioid Industry created promotional material misrepresented as educational material; and disseminated this mis-education through all the modalities described above. Misleading concepts such as “pseudoaddiction” and “breakthrough pain” provide two prominent examples.
  - ii. Defendants mischaracterized addictive behavior as “pseudoaddiction.”
    - A. Based on a single case report of a patient who engaged in drug-seeking behavior,<sup>405</sup> doctors were encouraged to conceptualize the patient’s addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox. The authors of the case report incorrectly asserted that treatment of pain is often inadequate because of “excessive fears of tolerance and dependence by both health professionals and the public,”<sup>406</sup> when in fact those fears are well-justified and should be respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly puts more patients at risk of becoming addicted or dependent.
    - B. There is no such thing as “pseudoaddiction,” and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.
    - C. As stated in an article by Dowell and Kunins, pseudoaddiction is neither scientific nor a clinically valid construct: “Some authors have stated that behaviors such as taking more opioids than prescribed may represent pseudoaddiction, a concept introduced in a case report in 1989 as “abnormal behavior developing as a direct consequence of inadequate pain management.” However, this concept remains untested, without scientific studies validating diagnostic criteria or describing long-term clinical outcomes. Nonetheless, some

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<sup>405</sup> Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989; 36(3):363-366. <http://www.ncbi.nlm.nih.gov/pubmed/2710565>.

<sup>406</sup> *Id.* at p. 365.



pain societies have promoted this concept and suggest that some patients demonstrating behaviors typical of opioid addiction may actually require higher doses. Rather than representing iatrogenic undertreatment of pain, however, behaviors described as pseudoaddiction may represent predictable responses to opioid exposure. Long term opioid use typically results in tolerance. A standard clinical solution is to increase opioid dose. However, contrary to the view that there is no maximum safe dose if opioids are increased gradually over time, death from opioid overdose becomes more likely at higher doses.”<sup>407</sup>

- D. In a review article on use of the term “pseudoaddiction,” the authors found, “By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction. In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct.”<sup>408</sup> Further, the authors wrote, “In conclusion, we find no empirical evidence yet exists to justify a clinical ‘diagnosis’ of pseudoaddiction.”<sup>409</sup> I agree that there is no empirical evidence to justify a diagnosis of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.
- E. To “correctly define addiction,” PPSG took consensus definitions from the Pharmaceutical-Opioid-Industry-funded ASAM, AAPM, and APS.<sup>410</sup> Those included a definition of the term pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may ‘clock watch,’ and may otherwise seem inappropriately ‘drug seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be

<sup>407</sup> Dowell *et al*, “Risky Drugs”, fn. 52, above, at p. 2219.

<sup>408</sup> Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction? An Investigation of the Medical Literature. *Curr Addict Rep* 2015;310-317. doi:10.1007/s40429-015-0074-7, at p. 310.

<sup>409</sup> *Id.* at p. 314.

<sup>410</sup> WIS\_PPSG\_002042, June 8, 2001.

distinguished from true addiction in that the behaviors resolve when pain is effectively treated.”<sup>411</sup> Thus, PPSG, an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of “pseudoaddiction” as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report). Dr. Portenoy later criticized the Pharmaceutical Opioid Industry’s use of the term pseudoaddiction.<sup>412</sup>

- F. The 1998 Industry-influenced guidelines of the FSMB incorporate the concept of pseudoaddiction,<sup>413</sup> providing further evidence of industry’s influence over the FSMB.

iii. Defendants mischaracterized tolerance as “breakthrough pain”

- A. “Breakthrough pain” is a term used by the Pharmaceutical Opioid Industry to describe a heightened state of intermittent pain that exceeds the analgesic capacity of the patients’ underlying chronic opioid dose. In fact, “breakthrough pain” is far more likely to represent the patients’ declining response to their prescribed opioids due to the well-established effect of tolerance, whereby a greater opioid dose is needed to attain the same effect over time. The addition of ACTIQ or other opioids for so-called “breakthrough pain” represents an increased opioid dose that adds to patients’ risk of adverse effects.
- B. Tolerance is the need for more and more of the drug to get the same effect. As the opioid dose is increased to overcome tolerance to the pain-relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with opioids, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.<sup>414</sup> Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite

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<sup>411</sup> *Id.*

<sup>412</sup> Declaration of Russell K. Portenoy, M.D. in MDL 2804, at ¶ 44.

<sup>413</sup> Federation of State Medical Boards. *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (May 2, 1998), [https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model\\_0.pdf](https://painpolicy.iu.edu/sites/default/files/sites/www.painpolicy.wisc.edu/files/model_0.pdf).

<sup>414</sup> Lembke, *et al.*, “Weighing the Risks,” fn.5, above, at p. 987; Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. *Evid Rep Technol Assess* (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPERTA218, at p. ES-25.

tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose.

- C. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990s and early 2000s, Defendants' promotional messages advised doctors that tolerance should be addressed by adding short-acting opioids to long-acting opioids for "breakthrough pain," or by "rotating" to another opioid.
- D. However, "There is fair evidence that long-acting opioids and a combination of long-acting and short-acting opioids contribute to increasing fatalities and that even low-doses of 40 mg or 50 mg of daily morphine equivalent may be responsible for emergency room admissions with overdoses and deaths."<sup>415</sup> Further, "Higher doses and a combination of short-acting and long-acting opioids are likely to lead to abuse, and also cause serious dose-related adverse effects including death."<sup>416</sup>
- E. As explained more fully in Appendix I.B. to this Report, Defendants marketed opioids such as ACTIQ as "the ideal agent" for breakthrough chronic pain.<sup>417</sup> This promotional message was misleading and contributed to opioid over-exposure.
  - o. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals and patients in order to increase sales of prescription opioids that resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, others bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility for its role in promoting false messages of substantial benefit and

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<sup>415</sup> Manchikanti L, *et al.* American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 1 – evidence assessment. *Pain Physician*. 2012;15(S1):S1-S66, at p. S1.

<sup>416</sup> *Id.* at p. S10.

<sup>417</sup> TEVA\_CAOC\_00759630 at -9633.

low risk of opioids, and in then taking advantage of the demand they created by selling the excessive supply that fueled the epidemic.

- p. The Pharmaceutical Opioid Industry, including Defendants, succeeded in bringing about, and maintaining, a paradigm shift with respect to opioid prescribing since the mid-1990s. The risks of addiction were significantly downplayed, and the benefits, especially for long-term use, were greatly exaggerated. As a result of this paradigm shift, doctors were not able to make an informed risk-benefit calculation for opioid therapy, underestimating the addiction risks and overestimating the benefits of prescription opioids. This underestimation of risks and overestimation of benefits became widespread, based on the falsehoods and misrepresentations of the Defendants and others. Indeed, doctors were told that to withhold opioid therapy out of concerns about addiction would violate evidence-based treatment.
- q. Because Defendants were successful in bringing about the paradigm shift through a protracted and multi-faceted campaign of misrepresentations, it is not helpful to ask whether particular prescriptions written during this time period were “medically appropriate” or not. Most doctors undoubtedly believed that the prescriptions they were writing for opioids were “medically appropriate” under the new paradigm shift that resulted from Defendants’ successful promotion and marketing. Conversely, under the previous, and correct understanding of the risks and benefits of opioids, doctors would have prescribed opioids far less often, because the generally accepted risk/benefit balance weighed against opioids. The misrepresentation of opioid risks and benefits also resulted in opioids being prescribed for longer periods, with less scrutiny, and for a wider range of conditions, because doctors had been led to believe that addiction was not a serious concern, and that long-term opioid therapy was effective for chronic pain. Accordingly, the inappropriate three-to-fourfold increase since the mid-1990s did not transform into “medically appropriate” prescribing. Rather, the massive increase was caused by defendants’ misrepresentations contrary to the scientific evidence of significant risks and minimal benefits.
- r. My opinions stated above are consistent with, and supported by, the ASPPH Report referenced above, which found, “The medical community became more aggressive in its use of opioids in response to a multi-faceted pharmaceutical industry-funded campaign that downplayed opioid risks and exaggerated benefits,” and that “the opioid crisis was caused largely by deceptive marketing.”<sup>418</sup> The ASPPH Report also stated, “The opioid crisis can be directly tied to practices adopted and encouraged by opioid manufacturers and distributors. As such, the industry’s credibility is near zero . . . .”<sup>419</sup>

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<sup>418</sup> ASPPH Report, “Bringing Science”, fn. 24, above, at p. 7; emphasis added.

<sup>419</sup> *Id.* at 32.

**5. Opioid distributors collaborated with opioid manufacturers and pharmacies to promote sales of opioid pain pills. Such coordinated efforts included programs to give away free samples of opioids, coupons to discount opioids, and promotion of specific opioid products under the guise of education. These activities increased the population of opioid users, dose and duration of opioid use, and the risk of opioid misuse, addiction, dependence, and death.**

- a. Opioid distributors worked in close collaboration with opioid manufacturers and pharmacies to promote sales of opioid pain pills. The claim that distributors were indifferent transporters of opioid pain pills between manufacturers and pharmacies ('We're just the trucks') is refuted by the many documents demonstrating a coordinated partnership to promote prescription opioid consumption, as well as a quid pro quo reimbursement structure. At every step in the supply chain, money flowed. There was a coordinated, psychologically sophisticated effort which appeared on its face to be about helping patients save money, 'overcome barriers,' and 'adhere to medical treatment,' but was in fact an elaborate scheme designed to promote sales of specific opioid products.
- b. Distributors, manufacturers, and pharmacies collaborated to offer free and discounted samples of dangerous and addictive opioids. As any drug dealer can tell you,<sup>420</sup> free samples are a tried and true way to hook consumers and secure future sales. Further, once patients become dependent on opioids, their continued consumption is income and price sensitive, making them vulnerable to discounted products.
  - i. "When a reduction in income is anticipated, it is predicted that consumption will decrease. When subsidies are eliminated, the reaction is similar to a decrease in income."<sup>421</sup> By offering free samples for prescription opioids, the Opioid Pharmaceutical Industry created customers in the form of opioid-dependent patients, and then kept them coming back with discounted prices. I observed these economic factors exert their influence among my own patients. Prescription opioids and illicit heroin/fentanyl are interchangeable in terms of their addictive and euphoric effects, and my patients would commonly use whichever opioid was more readily available at the lowest price.
  - ii. McKesson collaborated with Janssen to give away free fentanyl, an opioid that is 50 times more potent than heroin. Branded advertisements

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<sup>420</sup> "Drug Dealer Admits to Giving Free Sample." [https://www.herald-dispatch.com/news/drug-dealer-admits-to-giving-free-sample/article\\_ce289f74-e9c3-58ce-8cce-d7483e774627.html](https://www.herald-dispatch.com/news/drug-dealer-admits-to-giving-free-sample/article_ce289f74-e9c3-58ce-8cce-d7483e774627.html); dealer "admitted he provided the free sample of drugs to secure future sales..."

<sup>421</sup> Roddy J, Steinmiller CL, Greenwald MK. Heroin purchasing is income and price sensitive. *Psychol Addict Behav.* 2011;25(2):1-14, at p.5

promoted the free-give-away of 5 x 25 mcg Duragesic fentanyl patches, claimed by submitting a voucher to McKesson.<sup>422</sup>

- iii. McKesson directly targeted patients as well as pharmacists. McKesson described its “US-based, healthcare-dedicated contact center”<sup>423</sup> which delivers “patient-centric behavioral coaching”<sup>424</sup> as part of its broader “Behavioral Call Campaign” wherein “Agents make outbound calls to patients in order to uncover personal barrier and provide appropriate messaging/content to help overcome those barriers.”<sup>425</sup> These efforts, claim McKesson, are “aligned to address Janssen’s needs.”<sup>426</sup>
- iv. McKesson partnered with Janssen to give away free and discounted Nucynta and Nucynta ER. A “Nucynta ER/Nucynta New 10 Free Pills Program” from September 1, 2011 to December 31, 2012, gave patients free drug.<sup>427</sup> Per this document, where the “10 Free Pills” program was in place, “Average monthly claims [went] up 198% over 2011.”<sup>428</sup> When an older “10 Free Pills” program was phased out, Nucynta claims went down.<sup>429</sup>
- v. McKesson’s Nucynta promotional programs also included a Pay No More Than \$25 voucher card and a \$20 off savings card.<sup>430</sup> As of the end of November 2010 there were 56,641 claims for the voucher card and 66,885 claims for the savings card.<sup>431</sup> McKesson’s pharmacy analysis for the voucher card identified Walgreens as the top pharmacy in claims processed with Walgreens accounting for nearly a quarter of all claims.<sup>432</sup>
- vi. McKesson collaborated with both manufacturers and pharmacies through its LoyaltyScript and TrialScript programs. The programs utilized trial offers, savings cards, and e-coupons to promote opioids including OxyContin, Butrans, Hysingla, Ultram ER, Magnacet and Nucynta.<sup>433</sup> Patients would redeem the manufacturer’s offer at the

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<sup>422</sup> MCKMDL00334317. On the back end, Janssen trained its sales reps to promote the free fentanyl patches to doctors, as discussed at Section §C.4.e.xii.

<sup>423</sup> JAN-MS-01071368 at -1428.

<sup>424</sup> *Id.* at -1427.

<sup>425</sup> *Id.* at -1426.

<sup>426</sup> *Id.* at -1424.

<sup>427</sup> *Id.* at -1399.

<sup>428</sup> *Id.* at -1401.

<sup>429</sup> *Id.* at -1408.

<sup>430</sup> JAN-MS-01130535

<sup>431</sup> *Id.* at -0545, -0554.

<sup>432</sup> *Id.* at -0547.

<sup>433</sup> MNK-T1\_0006717600; JAN-MS-01130535; MCKMDL00385864. Magnacet was a Mallinckrodt product, initially marketed in June 2007, that combined various doses of the opioid oxycodone with 400 mg of

pharmacy and then the pharmacy would submit claims for reimbursement to McKesson.<sup>434</sup> The LoyaltyScript program for Magnacet paid a \$50 benefit, and by August 2008 there were 6,946 total paid Magnacet claims.<sup>435</sup> Additionally, McKesson's own pharmacy analysis ranked Walgreens as number one in claims processed, accounting for more than a quarter of all claims.<sup>436</sup> McKesson also collaborated with Janssen on a Nucynta TrialScript Program that utilized voucher cards.<sup>437</sup> By the end of November 2010 there were 17,509 Nucynta TrialScript claims.<sup>438</sup> McKesson's pharmacy analysis ranked Walgreens as the top pharmacy in claims processed, with Walgreens accounting for 23% of claims.<sup>439</sup>

A. In 2011, McKesson reminded Johnson & Johnson that “just as the McKesson/J&J partnership dates back as far as 1939, the relationship between J&J and MPRS [McKesson Patient Relationship Solutions] dates back to the 1990s when we first implemented acquisition and adherence programs. Since then, our relationship has matured and flourished as we have had the pleasure of managing numerous J&J retention programs” including Nucynta IR TrialScript, Nucynta IR LoyaltyScript Pay No More Than \$25, Nucynta IR LoyaltyScript \$20 Savings Card.<sup>440</sup> McKesson went on to boast that their LoyaltyScript programs “*delivered an average of 2.4 times more prescriptions over 12 months than a control group of similar patients prescribed the same drug but were not in the program, in a recent study. The two Nucynta IR LoyaltyScript programs (Pay no more than \$25 and \$20 Savings Card) combined have produced close to 150,000 claims to date.*”<sup>441</sup>

vii. McKesson partnered with Purdue to distribute a “Butrans Savings Card.”<sup>442</sup> In the first 8 months of the McKesson/Purdue Butrans

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acetaminophen, *see* [https://www.biospace.com/article/releases/-b-mallinckrodt-b-launches-magnacet-tm-tablets-/#:~:text=The%20U.S.%20Food%20and%20Drug,moderate%20to%20moderately%20severe%20pain](https://www.biospace.com/article/releases/-b-mallinckrodt-b-launches-magnacet-tm-tablets-/#:~:text=The%20U.S.%20Food%20and%20Drug,moderate%20to%20moderately%20severe%20pain.). Operating through “MaxCare,” a Pharmacy Benefit Manager, Mallinckrodt offered a “Patient Assistance Program” that provided all doses of Magnacet, among other products, for a \$20 co-pay. *See* [https://www.rxhope.com/pap/pdf/mallinckrodt\\_pharma\\_0209.pdf](https://www.rxhope.com/pap/pdf/mallinckrodt_pharma_0209.pdf).

<sup>434</sup> MCKMDL00385864 at p. 2.

<sup>435</sup> MNK-T1\_0006717600 at \*4, \*7 (produced natively).

<sup>436</sup> *Id.* at \*14.

<sup>437</sup> JAN-MS-01130535.

<sup>438</sup> *Id.* at -0539-0540.

<sup>439</sup> *Id.* at -0541.

<sup>440</sup> JAN-MS-00864519 at -4521 (emphasis in original).

<sup>441</sup> *Id.* at 4522-4523. (emphasis in original)

<sup>442</sup> Purdue Pharma Butrans Product Alert, September 2011, [http://rphmail.com/ch/2011/butrans\\_101411.html](http://rphmail.com/ch/2011/butrans_101411.html). (last accessed Feb. 2., 2021)



Savings Card program, there were 18,930 Butrans Savings Card claims with 45% of redemptions at Walgreens pharmacies.<sup>443</sup>

- viii. Cardinal Health partnered with Actavis to promote Kadian co-pay assistance cards with up to \$50 savings on Kadian prescriptions, with “no expiration” date cards available in 2011.<sup>444</sup> Actavis expanded the Kadian coupon program in October 2011 with co-pay coverage up to \$1,200 per year.<sup>445</sup> The explicit goals of the program were to “Facilitate new therapy starts”<sup>446</sup> and “Increase the average length of therapy.”<sup>447</sup>
- c. Opioid distributors collaborated with opioid manufacturers to advertise specific opioid products.
  - i. AmerisourceBergen collaborated with Janssen to advertise Nucynta for a fee of \$10,000 for a 2 week marketing campaign: “Horizontal Banner Ad on ABC Order, the new product ordering and communication platform for AmerisourceBergen Drug Corporation customers.”<sup>448</sup>
  - ii. In a 2012 document titled “McKesson Manufacturer Marketing” McKesson described ways it could increase sales of opioids and maximize profits for ACTIQ and FENTORA, by “delivering an unmatched combination of communication, promotion, distribution options, plus targeted analytics of exclusive data, McKesson will enable Cephalon to set strategies that prioritize opportunities, optimize resources, and maximize profitability. McKesson partners with pharmaceutical manufacturers such as Cephalon to define and execute customized strategies targeting key awareness, sales, and distribution goals at all stages of the product life cycle.”<sup>449</sup> Cephalon was acquired by TEVA as of October 2011, shortly before McKesson prepared the “Manufacturer Marketing” proposal.<sup>450</sup>
  - iii. On January 25, 2012, McKesson partnered with TEVA to promote ACTIQ and FENTORA including an agreement to “distribute three (3) e-mail messages promoting the products identified below to 7,000 retail pharmacy recipients” and “four hundred sixty three (463) mailers to our

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<sup>443</sup> PPLPC004000291443.

<sup>444</sup> ACTAVIS0375300 and ACTAVIS0375303; *see also* ALLERGAN\_MDL\_01198205 and ALLERGAN\_MDL\_01198203.

<sup>445</sup> ACTAVIS0237771; *see also* ACTAVIS0190235 (Kadian “Save up to \$1,200” brochure)

<sup>446</sup> ACTAVIS0237771 at -7775.

<sup>447</sup> *Id.*

<sup>448</sup> ABDCMDL00002828.

<sup>449</sup> MCKMDL00353374 at -3376

<sup>450</sup> Teva completed its acquisition of Cephalon on October 14, 2011, *see*

<https://www.fiercepharma.com/pharma/teva-completes-acquisition-of-cephalon> (last accessed 10/22/2020)

- top Independent Pharmacies.”<sup>451</sup> The 2012 proposal and agreement between McKesson and TEVA demonstrates that McKesson was not just in the business of distribution but was actively engaged with manufacturers to find ways to sell more opioids.
- iv. Cardinal Health partnered with TEVA to promote TEVA products. Cardinal Health agreed to distribute, at Teva’s request, “one (1) e-mail communication to approximately 105,000 retail pharmacists and pharmacy technicians in Cardinal Health’s eConnection program database that includes information on the CII product launch.”<sup>452</sup> And “The communication distributed by Cardinal Health will be prepared by Teva in accordance with the specifications set forth below.”<sup>453</sup> Content “May include product benefits, ordering information and website links. Teva to provide the message to appear in the subject line of the email communication.” “The cost to distribute the above one (1) e-mail communication shall be Eighteen Thousand Dollars (\$18,000).”<sup>454</sup>
  - v. Cardinal Health partnered with Actavis to promote Kadian through eConnection blasts urging retail pharmacists and pharmacy techs to “Stock up now, order today!”<sup>455</sup> The Cardinal eConnection blasts were sent to approximately 98,000 pharmacists and pharmacy techs<sup>456</sup> and were part of an Actavis stocking campaign to take advantage of supply shortages of Embeda, another long-acting opioid.<sup>457</sup>
  - vi. McKesson Specialty Health Pharmaceutical & Biotech Solutions, LP, collaborated with Purdue Pharma to advertise Butrans Transdermal System in October 2016, for a fee of \$17,850. McKesson “agrees to post Supplier’s graphical ad with a link to Supplier’s Supplier Product website (<https://www.butrans.com>), on McKesson’s online ordering portal, McKesson Connect. The graphical ad will be posted for a total of four (4) weeks.”<sup>458</sup>
  - vii. AmerisourceBergen partnered with Purdue in 2008 to promote Oxycontin’s “new items and the Rebate program”.<sup>459</sup> AmerisourceBergen sent a mailing to over 5,500 retail accounts and an alert to AmerisourceBergen’s retail group and customer service

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<sup>451</sup> MCKMDL00353368 at 3368.

<sup>452</sup> CAH\_MDL2804\_00132726 at -2727.

<sup>453</sup> *Id.*

<sup>454</sup> *Id.*

<sup>455</sup> ACTAVIS0220239, *see also* ACTAVIS0554311, [http://rphmail.com/ch/2012/kadian\\_102312/printable.pdf](http://rphmail.com/ch/2012/kadian_102312/printable.pdf), and CAH\_MDL2804\_02954370.

<sup>456</sup> CAH\_MDL2804\_02958781 at -8782.

<sup>457</sup> ACTAVIS0375300 and ACTAVIS0375303; *see also* ACTAVIS0357313 at -7320.

<sup>458</sup> MCKMDL00353277

<sup>459</sup> PPLPC004000146529 at -6530.

managers providing information regarding Purdue's "new OxyContin strengths available to ABC customers and the special rebate offer available to purchase these new items."<sup>460</sup> The "rebate increases if you order multiple strengths" and discounts ranged from \$13-\$18 for each 15mg bottle to \$44-\$59 for each 60mg bottle of OxyContin.<sup>461</sup>

- viii. The opioid distributor Cardinal promoted Exalgo on pharmacy ordering platforms. As described in this email exchange between Cardinal executive Leslie Arend and Covidian executive Connie Kisinger on April 12, 2013, Cardinal's own legal team expressed reservations about ads promoting the opioid product Exalgo: "I received word late this morning that due to some things with the DEA, our legal team made several changes to marketing programs with controlled substances. While we can feature Exalgo on the ordering platform, it was deemed that it could only be prompted by a search key word of 'Exalgo'. The reason for this is legal has said that the pharmacist must actually be searching for the product in order to show the advertisement otherwise it may seem as though Cardinal Health is 'pushing' a controlled substance."<sup>462</sup>
- d. Opioid manufacturers and distributors worked together with pharmacies to market specific opioids at the pharmacy counter. Pharmacists were trained to influence patient demand under the guise of education and "medication adherence."<sup>463</sup>
  - i. In 2012, McKesson proposed that Janssen "enhance" its Nucynta free and discount pill programs by going directly to customers using face to face Motivational Interviewing at the "pharmacy counter."<sup>464</sup> Motivational Interviewing is a form of individual psychotherapy originally conceived to help addicted patients get into recovery. It is ironic that McKesson recommended using these techniques to *encourage* opioid consumption.
  - ii. McKesson's Pharmacy Intervention Program's stated goal was to "Increase patient adherence to prescribed drug therapy through a series of targeted 'behavioral modification' counseling sessions delivered at the pharmacy counter"<sup>465</sup> and a "Comprehensive McKesson team

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<sup>460</sup> ABDCMDL07337446

<sup>461</sup> ABDCMDL07337447 at -448

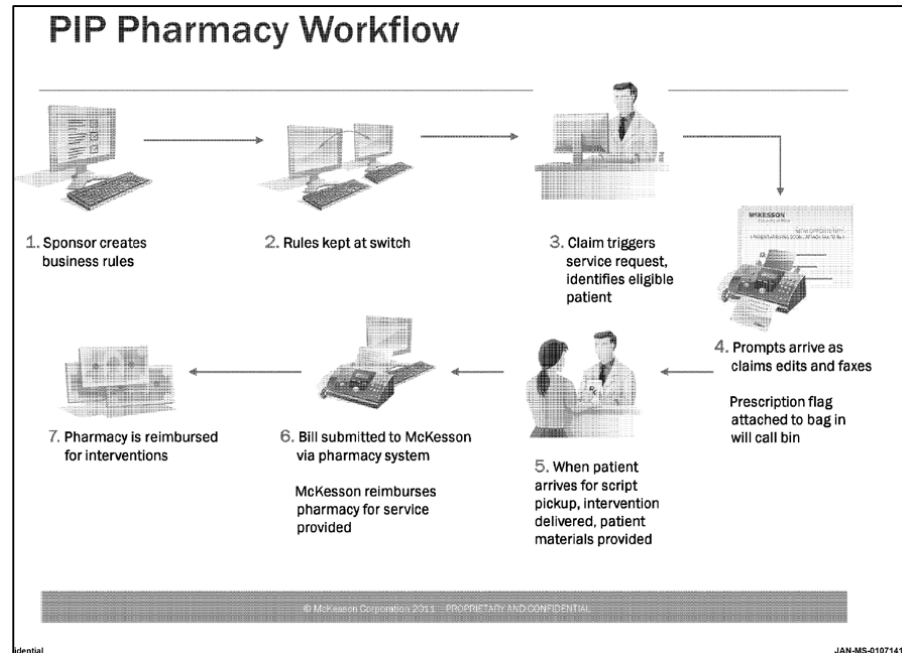
<sup>462</sup> MNK-T1\_0007819281

<sup>463</sup> Rollnick S, Miller W. What is Motivational Interviewing? *Behavioural and Cognitive Psychotherapy*. 1995;23(4):325-334.

<sup>464</sup> JAN-MS-01071368 at -1411-1416. McKesson implemented a similar program for Purdue's Butrans, *see* discussion at Section §C.5.e.

<sup>465</sup> *Id.* at -1416.

assembled to support pharmacy execution.”<sup>466</sup> The pharmacies, in turn, would be reimbursed for doing MI at “the pharmacy counter.” “McKesson reimburses pharmacy for service provided.”<sup>467</sup> The below McKesson slide shows how the Pharmacy Intervention Program (“PIP”) worked<sup>468</sup>:



- e. As stated by Lamkin and Elliott, “Of course, pharmaceutical adherence programs are not geared toward promoting patient health, but toward ensuring patients keep using a particular drug. As market research consultants Frost & Sullivan have acknowledged, ‘The most compelling reason to invest in these tailored communications is to increase return on investment (ROI) by keeping patients on the therapy longer.’ McKesson Patient Relationship Solutions assures pharmaceutical companies that the company’s ‘adherence tactics’ will ‘optimize the performance of your brand.’”<sup>469</sup> I agree with this view that pharmaceutical adherence programs are geared to increasing ROI and brand optimization, rather than promoting patient health. With respect to prescription opioids, chronic adherence conferred far greater risks than benefits, and such adherence harmed, rather than promoted, patient health.

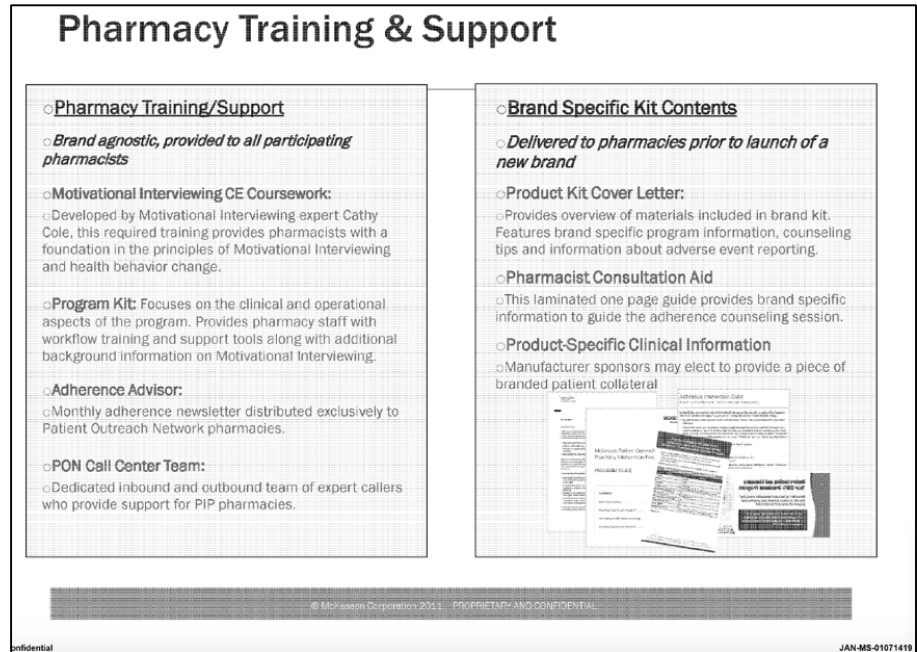
<sup>466</sup> *Id.*

<sup>467</sup> *Id.* at -1416-1417.

<sup>468</sup> *Id.* at -1417.

<sup>469</sup> Lamkin M, Elliott C. Curing the disobedient patient: Medication adherence programs as pharmaceutical marketing tools. *Journal of Law, Medicine and Ethics*. 2014;492-500, at pp. 498-499.

- i. Branded content was camouflaged inside non-branded “educational” content in the context of Motivational Interviewing. “Pharmacy Training/Support” including “Motivational Interviewing CE Coursework,” was paired with “Brand Specific Kit Contents” which included the following statement: “Manufacturer sponsors may elect to provide a piece of branded patient collateral.”<sup>470</sup> See below a graphic of the pharmacy Motivational Interviewing intervention:



- ii. In 2013, McKesson promoted its Pharmacy Intervention Program by letting Purdue know about their “Pharmacy Brand Kit,” whereby Purdue could promote its product under the guise of education: “The Brand Specific Pharmacy Kit is mailed to each participating pharmacies [sic] prior to launch. This kit includes a Cover Letter and Coaching Guide. Purdue will have the opportunity to participate in the development and review all pharmacy materials specific to their program. The brand kit can also include any additional resources the pharmacist should read as well as patient brochures to hand out during the coaching session (Purdue would develop and provide).”<sup>471</sup>
- iii. In other words, McKesson’s Pharmacy Intervention Program was a vehicle for opioid manufacturers to advertise their products directly to patient consumers through pharmacists.

<sup>470</sup> JAN-MS-01071368 at -1419.

<sup>471</sup> PPLPC002000140782 at -0783.

- iv. McKesson proposed to use its Pharmacy Intervention Program to increase opioid doses and thwart a trend they observed in 2013 in which patients were discontinuing opioids.<sup>472</sup> McKesson promoted maintaining and even increasing doses of Butrans: “In 2013, one of our commercial goals is to reduce discontinuation and improve patient adherence.... HCPs are initiating opioid-experienced patients inappropriately on the 5 mcg/hour when they should be initiated on the 10 mcg/hour. These factors are negatively impacting patient adherence, and Marketing would like to execute the McKesson Pharmacy Intervention Program in order to reduce the Butrans discontinuation rate.”<sup>473</sup> As of April 2014, more than 675 Butrans PIP coaching sessions had been delivered to patients.<sup>474</sup> Many patients on opioids at this time had good medical reasons for discontinuing opioids, including adverse medical consequences and serious risk of addiction and overdose death. Instead manufacturers, distributors, and pharmacies used “improving patient adherence” as a proxy for maintaining opioids.
- f. I am familiar with the MDL reports of Carmen Catizone, Craig McCann and James Rafalski on the subject of opioid dispensers, distributors and red flags indicating on-going diversion.<sup>475</sup> It is particularly persuasive that distributors and pharmacies such as McKesson, AmerisourceBergen, Cardinal, CVS, Walgreens and others have paid millions in settlements indicating their diversion systems failed.<sup>476</sup> Rafalski’s conclusions are consistent with my own opinions based on my review of the documents described above, that is, the Opioid Distributors collaborated with manufacturers and pharmacies to increase sales and patient exposure, while failing to implement meaningful systems to monitor or control rampant diversion and oversupply of opioids.

**6. Pharmacies leveraged their unique and pivotal position in the opioid supply chain to contribute to the unprecedented and unchecked flow of opioid pain pills into the community. They alone had direct contact with opioid manufacturers and distributors upstream, and patients and prescribers downstream. Their coordinated efforts included direct mailings and media campaigns, continuing medical education courses for pharmacists, partnering with pro-opioid industry advocacy and lobbying organizations, and creating stores where prescription opioids were readily available and abundant, sometimes called “Super Stores.” They ignored ‘red flags’ for misuse and diversion (including concerns expressed by their own pharmacists), and failed to provide**

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<sup>472</sup> PPLPC002000140782

<sup>473</sup> *Id.*

<sup>474</sup> PPLPC017000552799

<sup>475</sup> See e.g., Expert Report of Carmen Catizone, *City and County of San Francisco v. Purdue Pharma*, No. 3:18-cv-7591 (Oct. 5, 2021). (hereinafter, “Catizone Report”); Expert Report of Craig J. McCann, *City and County of San Francisco v. Purdue Pharma*, No. 3:18-cv-7591 (Oct. 5, 2021). (herein after “McCann Report”); Expert Report of James Rafalski, *City and County of San Francisco v. Purdue Pharma*, No. 3:18-cv-7591 (Oct. 5, 2021). (hereinafter “Rafalski Report”).

<sup>476</sup> Rafalski Report, pp. 25-36. See also Section 6 of this report, addressing fines and penalties imposed on Pharmacy Defendants for violations of the CSA.



**pharmacists with sufficient time, resources, or incentives to investigate red flags. They also failed to use or analyze their own dispensing data to assist pharmacies in identifying red flags. By increasing and assuring the supply of opioids, and failing to provide effective controls against diversion, pharmacies contributed to opioid misuse, addiction, dependence, and death.**

- a. I have read the Findings of Fact and Conclusions of Law issued by Judge Breyer in the San Francisco opioids litigation dated August 10, 2022, and the Findings are consistent with the opinions that I have developed through review of many of the same documents referenced in this Report.
- b. Pharmacies occupy a unique and pivotal position in the opioid supply chain.
  - i. Pharmacies, unlike other defendants in this litigation, had regular and direct contact with upstream and downstream suppliers (manufacturers, distributors, and prescribers) as well as face-to-face contact with patients themselves. As such, they were in the unique position of influencing the opioid supply chain at every level, from the corporate to the individual. Evidence shows that Kroger pharmacy bonuses in 2006 were based in part on pharmacist's direct detailing to individual local physicians and doctor's offices to promote the benefits of their pharmacy.<sup>477</sup>
  - ii. The unique and influential role that pharmacists play today is well-captured by Lamkin and Elliott's article on the role of pharmacies as marketing tools: "Like nurses, pharmacists have become 'a key cog in not only the pharmaceutical chain, but also in the marketing of prescription drugs and services.' Pharmacists are effective at improving adherence because patients trust them, ranking pharmacists second only to nurses in terms of professional ethics and honesty. In addition, patients interact more with pharmacists than any other health care professional. So pharmacists have many opportunities to influence patients and identify the reasons individual patients are not taking their medications. As pharmaceutical distributor McKesson says, pharmacists can offer 'personalized messaging, program enrollment, behavioral coaching and other clinical services at the point of dispensing.'"<sup>478</sup> Trust in pharmacies is misplaced when their actions are directed at increasing return on investment rather than patients' legitimate medical needs.
  - iii. The CDC has stated that because pharmacists are "[o]n the front lines of dispensing opioid pain medications and providing medication-related

<sup>477</sup> Deposition Transcript of Ryan Davis, June 10, 2022. In Re: National Prescription Opiate Litigation, Case Track 7 (Case No. 1:17-MD-2804), at 252:6-12; *see also* Davis Ex. 8, (KrogerMDL00000083).

<sup>478</sup> Lamkin, "Curing the Disobedient Patient," fn. 469, above, at p. 495. (internal citations omitted)



services, pharmacists can serve as a first line of defense by engaging in prevention and treatment efforts of opioid use disorder and overdose.”<sup>479</sup>

- iv. Pharmacists and pharmacies have information that physicians don’t have concerning “red flags,” including but not limited to the following: a patient who pays in cash for the prescription, travels a far distance to fill a prescription, fills multiple prescriptions simultaneously for the same or similar drugs, fills multiple prescriptions that are dangerous in combination (opioids with benzodiazepines, and/or the “holy trinity” i.e. opioids, benzodiazepines, and muscle relaxants or other central nervous system depressants), and/or appears under the influence of an intoxicant at the time of filling.<sup>480</sup> Pharmacy Defendants in this case also had access to their own chain-wide prescribing data that could have been analyzed to identify prescriber-related red flags that could have prevented substantial diversion, such as repeatedly combining dangerous medications, prescribing excessive doses, and prescribing outside of legitimate medical indications or not in the usual scope of clinical practice. Pharmacists and pharmacies have a duty to patients and the public interest to act on that information. They are also required to do so by the Controlled Substances Act.
- c. Direct mailings and media campaigns: Pharmacy Defendants collaborated with opioid manufacturers and distributors to spread misinformation about the safety and efficacy of opioid pain pills through direct-mailing and media campaigns targeting their own pharmacists as well as patient consumers.
  - i. Agreements between Walgreens and several manufacturers, including Purdue, Janssen, Abbott Labs, and Mallinckrodt between 2008 and 2012, provided for Walgreens to receive payments of \$25-\$30,000 from the manufacturers in exchange for Walgreens’ distribution of “Manufacturer Product Updates” (MPUs) to Walgreens’ approximately 26,000 pharmacists.<sup>481</sup> In return, Walgreens provided Purdue with data on OxyContin purchases “at the store level.”<sup>482</sup> The MPUs used “content provided by Client,” i.e., the manufacturer, to “educate” Walgreens’ pharmacists.<sup>483</sup> Walgreens further stated that “PI [Package Insert] Reports may also be utilized as a tool to assist pharmacies in making sound, clinical decisions when dispensing these medications.”<sup>484</sup> In other words, these reports do not serve merely to

<sup>479</sup> Centers for Disease Control and Prevention. Pharmacists: On the front lines. (Oct. 17, 2016), [https://www.cdc.gov/drugoverdose/pdf/pharmacists\\_brochure-a.pdf](https://www.cdc.gov/drugoverdose/pdf/pharmacists_brochure-a.pdf) (last accessed Jan. 15, 2021)

<sup>480</sup> WAGMDL00254700, at -4701-4702.

<sup>481</sup> PPLPC031001349535; WAGFLAG03915801; WAGFLAG03916473; WAGFLAG03916482; WAGFLAG03916483.

<sup>482</sup> *Id.*

<sup>483</sup> Shah Deposition Ex. PXWAG-576, at WAGFLAG03915801. (February 1, 2008).

<sup>484</sup> *Id.*

notify pharmacists of new products or dose formulations. They acknowledge that pharmacists play a crucial role in clinical decision-making and are influenced by the clinical decision-making guidelines in these opioid manufacturer-created and Walgreens-disseminated documents.

- ii. Walgreens was aware of opioid manufacturers' financial interest in the issuance and timeliness of MPU distribution.
  - A. Purdue's Tony Scifo contacted Walgreens "at least weekly" to complain that Walgreens pharmacists were not stocking or filling Hysingla prescriptions in 2015.<sup>485</sup> Scifo insisted that Walgreens needed to send the Hysingla MPU and Pharmacists Guide to its pharmacists, evincing an expectation that the MPU would raise Walgreens' pharmacists' awareness of the product and thereby increase dispensing.<sup>486</sup>
  - B. Walgreens' employee Van Anderson, Director of National Accounts, stated that they "can understand the concern" since Purdue wanted the MPU to go out "in time to impact launch" of the new product.<sup>487</sup>
  - C. In other words, opioid manufacturers were willing to pay Walgreens for the MPUs described above, because they expected the MPUs to increase dispensing, sales and profits. Walgreens, in turn, benefitted from the manufacturers' repeated payments for the distribution of the MPUs, which worked as advertising of the products to pharmacists, in much the same way that direct-to-consumer ads increase sales by raising consumer awareness of such products.<sup>488</sup>
- iii. Walgreens promoted opioid products directly to consumers at the pharmacy counter.
  - A. A March 8, 2002 direct-to-consumer advertisement shows that Walgreens cooperated with Janssen, the manufacturer of Duragesic, to include positive messaging about fentanyl patches in comparison to oxycodone pills directly to customers filling OxyContin (and other oral opioid

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<sup>485</sup> Shah Deposition Tr., 132:21-142:15; Shah Deposition Exs. PXWAG-584, 585, 586.

<sup>486</sup> *Id.*

<sup>487</sup> *Id.*

<sup>488</sup> *See, e.g.*, Kaiser Family Foundation. Impact of Direct-to-Consumer Advertising on Prescription Drug Spending. (June 2003), <https://www.kff.org/wp-content/uploads/2003/06/6084-impact-of-direct-to-consumer-advertising-on-prescription-drug-spending-summary-of-findings.pdf>, at p. 1.

prescriptions) as part of a customer's prescription enclosure.<sup>489</sup> This demonstrates that Walgreens was actively involved in promoting and advertising specific opioid products at the pharmacy counter. The prescription enclosure states "Patients Prefer The Duragesic Patch."<sup>490</sup>

- B. This direct-to-consumer advertisement, "which Janssen pays pharmacists to enclose [with] prescriptions filled for OxyContin Tablets and other oral opioid products"<sup>491</sup> states that Duragesic should be used for "severe pain that will last more than a few days (chronic pain)."<sup>492</sup> No definition of chronic pain is consistent with this statement. Instead, chronic pain is defined as pain that lasts over 90 days or longer than the healing time for tissue damage.
- C. The Janssen advertisement also states, "it's relatively rare for patients to become addicted to painkillers when used appropriately. Most abusers of these drugs are not patients, but instead people who obtain the pills without a prescription."<sup>493</sup> This is false and misleading in that addiction to prescription opioids is common, not rare, even when taken by patients as prescribed.<sup>494</sup> The most common way that people get misused opioids is directly or indirectly through a doctor's prescription.
- D. The Duragesic ad on an OxyContin prescription also illustrates that Walgreens was an equal opportunity opioid promoter, happy to play one opioid manufacturer off against the other as long as Walgreens was getting paid.

iv. CVS advertised specific opioid products at the pharmacy counter.

- A. In 2011 CVS published an "educational services" document describing a promotional campaign they could launch within CVS Caremark pharmacies on behalf of selected opioid manufacturers, for a fee.<sup>495</sup> This document illustrates that

<sup>489</sup> PPLPC051000013546. *See also*, PDD8013015138 at -5148. (April 2, 2002)

<sup>490</sup> PPLPC051000013546, at -3546.

<sup>491</sup> PDD8013015138.

<sup>492</sup> PPLPC051000013546, at -3547.

<sup>493</sup> *Id.* at -3548.

<sup>494</sup> Purdue agreed this was false and misleading in a June 24, 2002 letter to the FDA, stating that "The inference plainly intended is that abuse is not associated with Duragesic patches, so the patient has a reason to switch medications. This appears to contradict the Drug Abuse and Diversion section of the Duragesic package insert, and the many reports of abuse of fentanyl patches." *See* PDD8013015138 at -5138.

<sup>495</sup> INSYS-MDL-000422516

CVS Caremark was in the business of promoting opioids, not just dispensing them.

- B. The 2011 CVS document leads with the statement “Communicate your product’s unique clinical benefits to thousands of targeted individuals.”<sup>496</sup> On the second page of this document, next to a picture of a pharmacist talking to two patient consumers, the document reads, “Get the medicine Right .... with the right educational communications.”<sup>497</sup>
- C. This document illustrates how CVS Caremark employed tactics initially introduced by Purdue Pharma to promote opioid products using targeted endorsements to specific patients under the guise of education. CVS courted opioid manufacturers with promises of “[i]dentifying patients who may benefit from your product,” increasing “awareness of new treatments or therapies,”<sup>498</sup> and a “Pharmacy Literature Display” to “[e]ducate patients via literature located adjacent to prescription counter.”<sup>499</sup> CVS Caremark used buzzwords like “education,” and “literature” to give their promotional efforts the sheen of science, without the substance of scientific accuracy.
- D. CVS offered these services to opioid manufacturers for a fee. A newsletter to pharmacies cost \$40,000.<sup>500</sup> Likewise, strategically placed information for patients “adjacent to prescription counter” cost \$220,000/mo for 7,300 store distribution.<sup>501</sup> CVS also engaged in direct-to-consumer advertising: Patient direct mailers,<sup>502</sup> and “messaging” printed directly on customer prescription receipts, cost \$10,000 setup fee and \$0.20/print to allow for “targeting by product, fill or refill number, disease state or demographic selectors.”<sup>503</sup>
- v. Defendant pharmacies were active collaborators in coupon redemption programs and free product offers for opioid products.

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<sup>496</sup> *Id.* at -2517.

<sup>497</sup> *Id.*

<sup>498</sup> *Id.* at -2519

<sup>499</sup> *Id.* at -2522.

<sup>500</sup> *Id.* at -2521.

<sup>501</sup> *Id.* at -2522.

<sup>502</sup> *Id.* at -2525.

<sup>503</sup> *Id.* at -2524.

- A. In July 2004, Purdue launched a “stock and save” rebate program for 80mg OxyContin tablets to provide “customers with a significant cost savings” on high dose OxyContin. Kroger, Publix and other regional and chain pharmacies participated.<sup>504</sup> In 2011, Kroger, Publix and Albertsons received payments for participation in Purdue’s Butrans “Stock and Save Program” including \$8,268 paid to Albertsons for claims from multiple Sav-On pharmacy locations in Fort Worth and Arlington, Texas.<sup>505</sup>
- B. In 2006, 85% of all OxyContin coupon and savings card redemptions came from Walgreens and CVS.<sup>506</sup> Hundreds of OxyContin coupon and savings cards were also redeemed at Kroger, Publix and Albertson’s pharmacies.<sup>507</sup>
- C. For redemptions at Walgreens and CVS, “five states overlap in the top for both Florida, Ohio, Arizonian [sic], Indiana & Texas.”<sup>508</sup>
- D. In January 2009, CVS began implementing a “strategic partnering plan” with Janssen.<sup>509</sup> Highlights of this plan included collaboration in educational programs, trade shows, new opioid products (tapentadol) and the development of a patient resource binder which would allow “easy organization and access of all coupons, vouchers, and rebates. All [CVS] Supervisors agreed that this was a useful tool that would improve their current process. There was excitement around having this implemented in their top 100 locations. They envision having the data entry technician responsible for checking to see if a coupon/voucher/free trial offer is available. CVS agreed to produce a shelf label that will tell the pharmacist if there is a coupon available for that product in the Patient Resource Binder.”<sup>510</sup>
- E. In 2015, Kroger, Publix, and Albertson’s participated in Purdue’s “Free Trial Card” offer for Hyslingla ER.<sup>511</sup>

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<sup>504</sup> PURCHI-003288825 (Bard Deposition Ex. 4)

<sup>505</sup> PPLPC004000282746

<sup>506</sup> PPLPC004000089723 and PPLPC004000089725

<sup>507</sup> PPLPC004000089725

<sup>508</sup> *Id.*

<sup>509</sup> JAN-MS-00470438.

<sup>510</sup> *Id.* at -0439.

<sup>511</sup> PPLPC025000203443 (Bard Deposition Ex. 8)

- F. As discussed in §C.5.b., above, free samples are a tried and true way to hook consumers and secure future sales. Once patients become dependent on opioids, their continued consumption is income and price sensitive, making them vulnerable to discounted products.
- vi. Opioid manufacturers, including Purdue and Actavis, contracted with a company called Adheris for prescription adherence programs to be offered to retail pharmacy chains including Kroger, Publix and Albertsons for prescription opioids including Butrans and Kadian.<sup>512</sup> The goal of these programs was to improve patient adherence and increase overall length of therapy by providing patients “behavior-triggered refill reminders.”<sup>513</sup>
- A. A 2013 agreement between Purdue and Adheris detailed a year-long “DirectAdhere program” for Butrans with a goal “to improve patient adherence by providing patients with education on Butrans, disease state information, and timely, behavior-triggered refill reminders.”<sup>514</sup> The agreement notes that the program will be offered to the retail pharmacy chains in the “Adheris Pharmacy Network” which included Kroger and Publix.<sup>515</sup> The agreement called for 72,520 letters mailed to an estimated 19,600 Butrans patients.<sup>516</sup> The communications included a letter that: “...encourages patients to contact their physicians to determine whether another prescription is appropriate and/or provides the option to request that the pharmacist contact the physician on the patient’s behalf.”<sup>517</sup>
- B. “Approximately 6k pharmacies partnered with the Butrans DirectAdhere program” from Adheris, a direct-to-patient mail program including a Welcome Letter, an Enrollment Reinforcement Letter, Refill #1 Reminder Letter and a Next Rx Letter, that were mailed directly to the patient, at home, on the letterhead of their pharmacy.<sup>518</sup> The Butrans DirectAdhere

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<sup>512</sup> PPLP003358929; ALLERGAN\_MDL\_01890807 and PPLP003345164 at -5165.

<sup>513</sup> *Id.*

<sup>514</sup> PPLP003358929

<sup>515</sup> *Id.* at -8933, -8936.

<sup>516</sup> *Id.* at -8932.

<sup>517</sup> *Id.* at -8931.

<sup>518</sup> PPLPC017000552799.

program had a 2:1 ROI [return on investment] guaranteed in the contract.<sup>519</sup>

- C. “Actavis Kadian LLC” and “Adheris, an inVentiv health company”<sup>520</sup> signed a 2009 agreement for a year-long adherence program to “improve patient persistence and increase the overall length of therapy by providing patients with education on [Kadian], tips to help manage pain, and timely, behavior-triggered refill reminders.”<sup>521</sup> The agreement called for 37,500 projected letters mailed to an estimated 15,000 Kadian patients.<sup>522</sup> The program was to be offered to all the pharmacies in Adheris’ pharmacy network, including Kroger.<sup>523</sup>
- D. A six month analysis of an Adheris “Kadian Adherence Program” showed “strong adherence improvements compared to control patients” with 5.3 incremental capsules obtained per Adherence Program patient, Adherence Program patients were 5.2% more likely to remain on therapy, and 1.4% more likely to return with new prescription.<sup>524</sup>
- E. This adherence program, like the others, exposed greater numbers of patients to chronic opioids that conferred significant risks while conferring little, if any, benefit.
- d. Continuing Medical Education (CME): Pharmacy Defendants collaborated with opioid manufacturers and distributors to spread misinformation about the safety and efficacy of opioid pain pills through continuing education programs targeting their own pharmacists.
  - i. Walgreens collaborated with Purdue to provide multiple “educational” programs to pharmacists that promoted opioid use.
    - A. In a December 1998 letter to Walgreens Pharmacy Supervisor, Scott Diveney, R PH, Purdue offered to fund a Purdue-sponsored continuing education (CE) program for pharmacists entitled “Use of Opioids – A Pharmacists’

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<sup>519</sup> *Id.*, at -2800.

<sup>520</sup> Actavis also contracted InVentiv to employ a Kadian sales force. See §C.4.e.x, above

<sup>521</sup> ALLERGAN\_MDL\_01890807

<sup>522</sup> *Id.* at -0818.

<sup>523</sup> *Id.* at -0817, -0829.

<sup>524</sup> ALLERGAN\_MDL\_00221533 at -1534.



Responsibilities.”<sup>525</sup> Walgreens accepted Purdue’s offer for Purdue-funded education of their pharmacists.<sup>526</sup>

- B. In an August 1999 letter to Walgreens Pharmacy Supervisor, Scott Diveney, R PH, Purdue offered to fund a Purdue-sponsored continuing education (CE) program for pharmacists entitled “Current Trends and the Pharmacist’s Role in the Treatment of Chronic Non-Malignant Pain.”<sup>527</sup>
- C. Walgreens entered into multiple agreements with Purdue wherein Purdue provided the funding and paid speakers for continuing education pain management programs for Walgreens pharmacists. These included a January 19, 1999 program on “Use of Opioids – A Pharmacist Responsibilities” with Louis Saeger, MD<sup>528</sup> and an October 21, 1999 lecture for a Walgreens District Meeting on “Current Trends and the Pharmacist’s Role in the Treatment of Chronic Non-Malignant Pain” by Joanie Smoot, Pharm.D.<sup>529</sup>
- D. Arthur Lipman was a Professor at the College of Pharmacy and Pain Center at the University of Utah, and editor of the Journal of Pharmaceutical Care in Pain & Symptom Control, who received financial support from opioid manufacturers Janssen and Purdue.<sup>530</sup> Lipman acted as an expert witness for Purdue, was a member of Purdue’s Pain Advisory Board for more than a decade<sup>531</sup> and was a Purdue KOL who also conducted speakers training for nurses and pharmacists to be speakers on pain management.<sup>532</sup> Because of his credentials in the pharmacy field, Lipman had particular credibility as a pharmacy expert.
- E. One example of Lipman’s training for pharmacists in 2000 stated: “Myth: Opioids Cause Addiction, Dependence and

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<sup>525</sup> PKY180836236. Walgreens was not required to produce discovery prior to January 1, 2006 and the content of this CE was not available for my review. *See e.g.*, In re National Prescription Opioid Litigation (Case No. 1:17-MD-2804), Discovery Ruling No. 3, at p. 4. (7/7/2018).

<sup>526</sup> *See* signed agreement at PKY180836239.

<sup>527</sup> PKY180524065. Walgreens was not required to produce discovery prior to January 1, 2006 and the content of this CE was not available for my review. *See e.g.*, In re National Prescription Opioid Litigation (Case No. 1:17-MD-2804), Discovery Ruling No. 3, at p. 4. (7/7/2018).

<sup>528</sup> PKY180836236, PKY180836239.

<sup>529</sup> PKY180524065.

<sup>530</sup> PKY183265978, at -6009-6011.

<sup>531</sup> PKY183265978, at -6011.

<sup>532</sup> PKY181218532, at 8533.

Tolerance; These effects can occur; They are rare in patients who have pain to due to physiological causes.”<sup>533</sup>

- F. In cases of “pseudoaddiction” Lipman recommended, “increase the opioid dose by 50%; assure that breakthrough doses are available.”<sup>534</sup>
- G. Lipman estimated the prevalence of iatrogenic addiction in the range of 0.03%-0.12%.<sup>535</sup>
- H. In conclusion, Lipman urged his audience of nurses and pharmacists to “Refute Myths About Opioids” and stated that “addiction is exquisitely rare.”<sup>536</sup>
- I. In fact, the best and most reliable estimates show that the risk of addiction to opioids is 10-30% among patients treated for chronic pain, which means that prescription opioid addiction is very common among chronic pain patients, as discussed in Section §C.8.b-c, below.
- J. Lipman also co-authored an April 2000 continuing education program funded by Purdue Pharma titled “Use of Opioids in Chronic Noncancer Pain.”<sup>537</sup> This program, targeting pharmacists as well as prescribers, also misleadingly stated that “Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare.”<sup>538</sup>
- K. Several internal Purdue emails reference Lipman’s 2000 CE program being distributed to Walgreens district managers in different regions of the country.<sup>539</sup> In May 2001, a Walgreens Regional Manager agreed to Purdue’s distribution of 300 copies of Lipman’s presentation at a Walgreens meeting in Milwaukee.<sup>540</sup> Another email noted that a Walgreens district manager in Florida “would like to personally educate and mandate completion of our CE program by Lipman...He

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<sup>533</sup> *Id.* at 8535.

<sup>534</sup> *Id.* at 8536

<sup>535</sup> *Id.*

<sup>536</sup> *Id.* at 8545

<sup>537</sup> PKY181071048. On November 20, 2001, Purdue removed the program from circulation and field force use. PPLPC008000021637.

<sup>538</sup> PKY181071048, at -1055.

<sup>539</sup> PPLPC008000016471, PPLPC024000044089, and PPLPC008000015992.

<sup>540</sup> PPLPC008000016471. Walgreens also agreed to Purdue’s distribution of 300 copies of a Purdue-sponsored CE by Daniel Carr, discussed above at §C.4.g.

supervises 30 pharmacists in his territory.”<sup>541</sup> Another Purdue email about the Lipman CE reported a Walgreens district manager in Tennessee “was very pleased to hear we had a pain CE and he wants 150 of them so he can mail them to all the pharmacists in his district,” and noted “[t]his will help use gain a stronger alliance with Walgreens and help to fend off any remaining abuse issues that are going through their stores.”<sup>542</sup>

- L. Lipman’s CE lectures could and did significantly increase pharmacy sales of OxyContin. In March 2001, after a series of Purdue-funded Lipman lectures in 5 rural Utah towns sponsored by a regional pharmacy chain “the range of OxyContin sales increases was anywhere from *double* to *eight* times that of the average prior to the lectures.”<sup>543</sup>
- M. Prior to July 2001, the FDA-approved label for OxyContin stated that “Iatrogenic ‘addiction’ to opioids legitimately used in the management of pain is very rare.”<sup>544</sup> In July 2001, the FDA-approved label for OxyContin was changed to eliminate the text “is very rare” and was replaced with: “The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, *data are not available to establish the true incidence of addiction in chronic pain patients.*”<sup>545</sup> Despite the change, the Lipman CE materials remained effective at Walgreens until April 1, 2002 and continued to spread the misleading message that iatrogenic addiction to opioids in chronic pain patients is “exquisitely rare”<sup>546</sup> with no evidence that Walgreens educated its pharmacists to correct the misinformation.
- N. In 2001, Purdue and Walgreens discussed collaborating on 5 hour CE programs over 4 days in Chicago, Illinois. Walgreens executive Dawn DiLuillo, Director of Recruitment and Trade Relations “also requested that if possible a few patients on high dosages of OxyContin should attend the meetings. They could relate to the audience their experience

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<sup>541</sup> PPLPC024000044089 at -4090.

<sup>542</sup> PPLPC008000015992.

<sup>543</sup> PPLPC008000015396, at -5397 (emphasis in original)

<sup>544</sup> PPLP004497026

<sup>545</sup> United States General Accounting Office. OxyContin Abuse and Diversion and Efforts to Address the Problem. (Publication No. GAO-04-110,) (December 2003), Appendix II, at p. 49. (emphasis added)

<sup>546</sup> PKY181071048, at -1049 and -1055.

with pain and give testimonials on how OxyContin has made a difference in their lives.”<sup>547</sup>

- O. In 2001 and 2002, Purdue sponsored and promoted “Should I Dispense This?” continuing education programs to pharmacists, including at Walgreens.<sup>548</sup> The presentations promoted the concept of “pseudoaddiction” and included a slide titled “The truth behind the fears: trends in opioid use and abuse” which stated that “the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse”<sup>549</sup> citing as support a study written by consultants and speakers for Purdue Pharma and Janssen Pharmaceuticals.<sup>550</sup>
- P. These Purdue sponsored continuing education materials provided misinformation to pharmacists concerning the false assertions of the low risk and great benefits of opioids, with Walgreens’ enthusiastic cooperation. The materials also included a multiple choice test at the end of the class which emphasized the misleading messages about opioids for pharmacists.<sup>551</sup> Later emails endorsed these programs, with one Purdue sales executive noting that “The absolute last thing we want is for the OxyContin prescription to be bounced out at the pharmacy level because of unfounded fears from the ‘uneducated’ pharmacist.”<sup>552</sup>
- ii. Walgreens collaborated with Endo Pharmaceuticals to spread misinformation to their pharmacists about opioids and increase dispensing of opioid products.
  - A. A 2012 on-line CE for pharmacists “Navigating the Management of Chronic Pain: A Pharmacist’s Guide” was

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<sup>547</sup> PPLPC008000020183

<sup>548</sup> PPLPC022000019177, PPLPC022000019178 and PPLPC036000008325.

<sup>549</sup> PPLPC022000019178 (produced natively), at \*38; PPLPC022000019179 (produced natively), at \*36.

<sup>550</sup> Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710-1714, at p. 1710. Joranson and Dahl are also discussed at above at §C.4.1., and below at Appendix II. The article cites the following conflicts of interest: “Financial Disclosures: Mr Joranson receives honoraria from Knoll Pharmaceutical, Purdue Pharma, and Janssen Pharmaceutical. He also receives unrestricted grants from Knoll Pharmaceutical and Purdue Pharma and is a consultant for Purdue Pharma. Dr Dahl serves on the Speakers Bureau for Purdue Pharma and is a consultant for Knoll Pharmaceuticals”

<sup>551</sup> See, e.g., PPLPC024000044089 at -4090.

<sup>552</sup> PPLPC029000019201 at -9201.

sponsored by Endo and available through the “CE Search Engine.”<sup>553</sup>

- B. Endo’s CE stated that full agonist opioids “have a potentially unlimited dose response and, thus, a theoretically unlimited dosing ceiling. In practice, however, patients often experience significant adverse effects as opioid doses increase. (Table 2).”<sup>554</sup>
- C. Table 2 lists significant adverse effects as constipation, nausea/vomiting, sedation/mental clouding and agitation/confusion<sup>555</sup> while failing to mention or list perhaps the most significant adverse effect of all: the significantly increased risk of addiction and death that comes with higher doses.
- D. The Endo CE noted that “[i]n a departure from previous guidelines, The American Geriatrics Society (AGS) now recommends a trial of opioids be considered for older patients with moderate-to-severe pain.”<sup>556</sup> What the CE did not note, however, was that the American Geriatrics Society received \$6,500 from Endo in 2000 alone and more than \$1.3 million from Endo, Purdue and Johnson & Johnson from 1997-2012.<sup>557</sup>
- E. Endo’s CE to pharmacists went on to introduce the term “opiophobia” to describe the “various fears and prejudices associated with the use of opioid analgesics which seems to unnecessarily limit the use of this class of medication,” and recommended that “A good understanding of terms such as pseudoaddiction and pseudotolerance will assist clinicians with educating colleagues and patients about the proper use of these analgesics.”<sup>558</sup> (see discussion of ‘pseudoaddiction’ at Section §C.4.n, above).

- iii. Walmart collaborated with Purdue to provide multiple “educational” programs to pharmacists that promoted opioid use.

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<sup>553</sup> WAGMDL00766955; *see also* WAGMDL00659802 at -9809.

<sup>554</sup> *Id.* at -6962.

<sup>555</sup> *Id.*

<sup>556</sup> WAGMDL0076695, at -6962.

<sup>557</sup> US Senate Finance Committee, “Findings”, fn. 368, above, at Appendix A.

<sup>558</sup> WAGMDL00766955, at -6962-6963.

- A. A July 1996 document detailed a Purdue-sponsored continuing education program for Walmart pharmacists entitled “New Trends in the Use of Opioids in Pain Management.”<sup>559</sup> Purdue paid Walmart \$20,000 in “educational grants” for this program.<sup>560</sup> Presenters received honoraria for \$1,000.<sup>561</sup> The program was expected to reach 2,125 stores with 200-300 live attendees and 500 remote viewers.<sup>562</sup>
- B. The “New Trends” course program, which was delivered to Walmart pharmacists and elsewhere, was replete with misleading messages about opioids, taught by individuals who were on Purdue’s speaker bureau and receiving consulting fees from opioid manufacturers.<sup>563</sup> Neil Irick, MD, one of the presenters of the “New Trends” CME to Walmart pharmacists was on Purdue’s Speaker’s Bureau, which means he had been trained by Purdue on course content and paid to deliver that content.<sup>564</sup>
- C. For example, in 1997 Neil Irick again presented on “New Trends for the Use of Opioids in Pain Management.” In that lecture, also sponsored by Purdue, Irick said that the best way to treat pain was to “[r]ealize that drugs and doctors do not cause drug addiction” and “[a]dmit that true addiction is much less of a problem than presumed.”<sup>565</sup> By minimizing the risks of opioids and iatrogenic addiction, Irick’s message represented a radical departure from evidence and practice prior to 1990.
- D. At the invitation of a Walmart pharmacist, acting in his capacity of the President of the Treasure Coast (Florida) Pharmacist Association, Purdue sponsored and presented a continuing education program to that association in November 1999, entitled, “Use of Opioids in Chronic Cancer and Non-Cancer Pain Management: The Myths and Realities.”<sup>566</sup> The Purdue sales representative noted, “This program represents a huge opportunity for Purdue since 100 pharmacists from the Treasure Coast area of Florida will be in attendance.

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<sup>559</sup> PKY180257493

<sup>560</sup> PKY180794346, at -4346.

<sup>561</sup> *Id.*, at -4353-4354

<sup>562</sup> *Id.*, at -4346.

<sup>563</sup> PKY180960389, at -0389-0395

<sup>564</sup> PKY180257493; PKY180960389 at -0394.

<sup>565</sup> PKY180960389 at -0410.

<sup>566</sup> PKY180512514 at 2515

Pharmacists from retail and hospital pharmacies (including Hospital Pharmacy Directors and retail pharmacy managers) in the Treasure Coast area (which includes the area from Sebastian to Jupiter, FL) are members of the association. This lecture will not only be key in educating pharmacists on the role of opioids in pain management and why OxyContin (and Palladone XL) are the best choices of opioid analgesics, but also improving the potential of Palladone XL<sup>567</sup> being placed on area hospital formularies.”<sup>568</sup>

- E. This document not only illustrates that Purdue promoted OxyContin by ‘teaching’ pharmacists that “OxyContin (and Palladone XC) are the best choices of opioid analgesics;” it further demonstrates the critical role that hospital formularies played in promoting certain opioid products. Once a drug is on a hospital formulary, it becomes the go-to drug for the high volume of opioids used within hospital systems. This top-down impact on large integrated health care systems cannot be overestimated. Hospitals and health care systems are training grounds for residents and medical students. It is well known within the medical profession that the skills and practices students and residents learn during their training, are the habits they take with them out into the world, wherever they end up practicing. Hence, hospital formularies have a lasting impact on how and what doctors prescribe.

- iv. CVS collaborated with Purdue to provide multiple “educational” programs to pharmacists that promoted opioid use.

- A. In April 2000, CVS sought to expand CE programs with Purdue “so that a greater number of their pharmacists will be able to attend.”<sup>569</sup> Purdue noted that “The timing is excellent with the approval of the 160mg” OxyContin and that “it is my hope that we can make CVS a ‘preferred supplier’” in the area.<sup>570</sup>
- B. On May 2, 2001 senior executives at Purdue met with “key pharmacy people at CVS.”<sup>571</sup> The stated goal of the meeting

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<sup>567</sup> Palladone was a Purdue hydromorphone product that was removed from the market by agreement with the FDA, because of a high risk of mortality with even small amounts of alcohol that caused its opioid dose to be administered in a short time. See Peck, P., “FDA, Maker Agree to Pull Palladone Pain Killer.” MedPage Today, (July 15, 2005). <https://www.medpagetoday.com/primarycare/preventivecare/1364>

<sup>568</sup> PKY180512514 at 2519.

<sup>569</sup> PPLPC024000013990, at -3991

<sup>570</sup> PPLPC024000013990

<sup>571</sup> PDD1701046870.



was to “talk about mutually beneficial initiatives with CVS to improve education with their pharmacists. We also wanted to reiterate our position on ensuring availability of OxyContin for appropriate patients.”<sup>572</sup> Note the use of the phrase “mutually beneficial initiatives,” illustrating the implicit quid pro quo which characterized many of these meetings between opioid manufacturers and pharmacies.

- C. A memorandum summarizing the meeting described that the “key pharmacy people” were “resolute in their commitment to good pharmacy practice,” which included “ensuring availability of OxyContin.”<sup>573</sup> Also, “As a group they were vocal, particularly Barry Jasilli [CVS, Director, Quality Improvement], indicating that they felt that Purdue was in many ways being victimized by the situation. That the product is not the issue, but that the abuser is the issue. He indicated that, from his perspective, we should be fighting back even harder.”<sup>574</sup>
- D. In the meeting, CVS agreed to post Purdue’s Abuse and Diversion brochure on their intranet site and send copies with personalized letters to 4,100 CVS pharmacists. Further, they discussed their “joint educational efforts,” “setting up at least five programs at this time through CVS,” “co-hosting programs in the areas of healthcare professionals”, and “CE programs.”<sup>575</sup>
- E. This memo unambiguously demonstrates that CVS cooperated with Purdue in their efforts to promote OxyContin, to depict the opioid epidemic as a problem of minority “abusers” rather than the more widespread problem of opioid oversupply, overdose fatalities, and addiction.
- F. Further, CVS’s promotion of Purdue’s Abuse and Diversion brochure - “How to Stop Drug Diversion and Protect Your Pharmacy”<sup>576</sup> - sidestepped the significant problem of patient consumers getting addicted through legitimate prescriptions. Contrary to Industry claims that addiction is “rare,” some 10-30% of chronic pain patients on long-term opioid therapy are addicted to opioids. Notably, it is telling that the document

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<sup>572</sup> *Id.*

<sup>573</sup> *Id.*

<sup>574</sup> *Id.*

<sup>575</sup> *Id.*

<sup>576</sup> PKY18028211

emphasized “how to ... protect your pharmacy” rather than focusing on how to protect patients.

- G. In August 2001, CVS wrote a letter to Purdue Pharma asking Purdue to fund an educational program they would deliver to pharmacists at their Marketing and Operations conference in Nashville, TN in September 2001.<sup>577</sup> In describing their proposed educational plan, they emphasized pharmacists’ “role change from one of a dispenser of products to that of a supplier of information, deliverer of medication, clinical reviewer of drug therapy, and even disease state manager.”<sup>578</sup> By virtue of this educational plan, CVS itself established that the pharmacists’ role went well beyond that of passive pill dispenser.
- H. CVS requested \$46,079 for the continuing education course for pharmacists,<sup>579</sup> which would include role playing opportunities on “how to handle situations which are often associated with Purdue’s products. By way of example: how to communicate effectively with patients and physicians about appropriate pain management therapy and how to resolve potential conflict with a drug ‘seeker’”.<sup>580</sup> Further, the memo touted CVS’ long history of having a positive relationship with Purdue, the benefits of the program to both organizations, and how the continuing education series would “contribute significantly to our strategic business goals.”<sup>581</sup>
- I. CVS’ memo reveals how well CVS understood the key role pharmacists play in influencing patients’ interactions with prescribers, and how CVS’s “strategic business goals” were linked to those of Purdue.
- J. Purdue produced a brochure titled “Counseling Patients & Their Families on the Role of Opioid Analgesics in Pain Management: A Pharmacist’s Guide” which contains misleading messages that “patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small”<sup>582</sup> and that “even patients undergoing long-term opioid therapy usually do not develop addictive

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<sup>577</sup> PPLPC008000019586, at 9587-9588.

<sup>578</sup> *Id.*, at -9586.

<sup>579</sup> *Id.*, at -9588.

<sup>580</sup> *Id.*, at -9586

<sup>581</sup> *Id.*

<sup>582</sup> PDD1501613462, at -3464 and -3470. [Scifo Deposition Ex. 6]

disorders.”<sup>583</sup> In 2002, it was provided to CVS,<sup>584</sup> Walgreens,<sup>585</sup> pharmaceutical distributors and others.<sup>586</sup>

- v. Kroger collaborated with Purdue to provide “educational” programs to pharmacists that promoted opioid use.
  - A. In 1997, Kroger representatives asked Purdue to provide speakers for the upcoming “Kroger Annual Pharmacy Conference,” expected attendance approximately 250 pharmacists.<sup>587</sup> Purdue recommended Dr. Art Lipman as speaker, among others.<sup>588</sup> As detailed elsewhere in this report, Dr. Lipman was the author of a CME program called “Use of Opioids in Chronic Non-Cancer Pain (CNCN),” which made the false claims, among others, that the majority of CNCN patients will experience significant improvement in pain after taking opioids, and that a very small minority will get addicted, citing to the erroneous datapoint of Porter and Jick.<sup>589</sup> Of note, in November 2001, a Purdue Sales Force Bulletin announced that Dr. Lipman’s “Use of Opioids in CNCN” would be removed from CME offerings.<sup>590</sup> Although records are not available to confirm that Lipman was the speaker at the Purdue-Kroger event, the messages conveyed by Purdue-sponsored speakers were generally the same as those conveyed by Lipman: false and misleading overstatements of benefits, along with false and misleading underestimates of the risks of addiction, dependence, overdose, and death.
  - B. In 2001, Kroger representative Doug Cornelius asked Purdue’s Don Tasser for 60 versions of Dr. Daniel Carr’s CME material entitled “The Impact of Chronic Pain” to disseminate to Kroger pharmacists.<sup>591</sup> Carr’s “Impact” states, “opioids are very unlikely to produce iatrogenic addiction,” contributing to

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<sup>583</sup> PDD1501613462, at -3464.

<sup>584</sup> PPLPC008000022279, at EXPORT ORG ACTIVITY tab, line 280. In July 2001, the FDA-approved label for OxyContin was changed to eliminate the text that iatrogenic addiction “is very rare” and was replaced with: “The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.”

<sup>585</sup> *Id.*, line 221.

<sup>586</sup> PPLPC008000022279, EXPORT ORG ACTIVITY tab.

<sup>587</sup> PPLPC024000001706

<sup>588</sup> PPLPC024000001706, at -1707.

<sup>589</sup> PKY181071048 at -1055.

<sup>590</sup> PPLPC008000021637.

<sup>591</sup> PPLPC008000021427, at -1428.

the false sense of safety of opioids that led pharmacists to ignore red flags of dispensing.<sup>592</sup>

C. In 2002, Purdue's Maribeth Kowalksi lectured Kroger's pharmacists on pain treatment in presentations titled "Should I Dispense This?" and "Pain Management for Pharmacists."<sup>593</sup> In 2003, Purdue's Greg Chudzik presented "Should I Dispense This?" to 300 Kroger pharmacists in Nashville, TN.<sup>594</sup> As described below, "Should I Dispense This?" promoted the concept of "pseudoaddiction" and included a slide titled "The truth behind the fears: trends in opioid use and abuse," which stated that "the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse"<sup>595</sup> citing as support a study written in 2000 by Joranson and others who were consultants and speakers for Purdue Pharma and Janssen Pharmaceuticals.<sup>596</sup>

D. Kroger subsidiary companies also allowed Purdue sales reps access to their pharmacy managers. On February 3, 2015 the Fred Meyer Pharmacy Sales Manager<sup>597</sup> wrote to Purdue's Tony Scifo "to strongly encourage you to attend our manager's meeting April 28<sup>th</sup> where your representatives will get dedicated time with each pharmacy manager and district manager to detail them on the benefits" of Hysingla ER.<sup>598</sup>

vi. Publix collaborated with Purdue to provide "educational" programs to pharmacists that promoted opioid use.

A. Documents produced by Purdue Pharma show collaboration with Publix on several CE programs in 2000 and 2003. A Purdue-produced "Publix Program Development Timeline"

<sup>592</sup> PKY180439662, at -9672.

<sup>593</sup> PPLPC008000038150, at Tab 2002. The false and misleading messages contained in "Should I dispense this?" are discussed at §C.6.d.i.O. and §C.6.d.v.C. and §C.6.e.i.; "Pain Management for Pharmacists" is discussed at §C.6.e.iii.

<sup>594</sup> PPLPC008000038150, at Tab 2003.

<sup>595</sup> PPLPC022000019178 (produced natively), at \*38; PPLPC022000019179 (produced natively), at \*36.

<sup>596</sup> Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710-1714, at p. 1710. Joranson and Dahl are also discussed at above at §C.4.l., and below at Appendix II. The article cites the following conflicts of interest: "Financial Disclosures: Mr Joranson receives honoraria from Knoll Pharmaceutical, Purdue Pharma, and Janssen Pharmaceutical. He also receives unrestricted grants from Knoll Pharmaceutical and Purdue Pharma and is a consultant for Purdue Pharma.

Dr Dahl serves on the Speakers Bureau for Purdue Pharma and is a consultant for Knoll Pharmaceuticals."

<sup>597</sup> Fred Meyer is a subsidiary of Kroger. See: <https://www.fredmeyer.com/i/kroger-family-of-companies>

<sup>598</sup> PPLPC023000754950 (Bard Deposition Ex. 7)

shows Purdue first met with Publix's Richard Gourash in April 2000 to "discuss Purdue's commitment to education and offer to provide a CE program on pain management for their pharmacists."<sup>599</sup> A September 2000 email thread discusses Publix's Manager of Integrated Care, Richard Gourash, meeting with Purdue's Dr. Jacqueline LaPerriere and Steve Bishop to set up CE programs in Florida (West Palm Beach, Orlando, and Tampa) and Atlanta, GA.<sup>600</sup> Steve Bishop notes that "this should really help us with Publix."<sup>601</sup> A March 2001, summary sheet for the "Publix Pharmacy Program Series" on the topic of "Pain Management: Legislative and Ethical Issues for Pharmacists" confirms programs on February 11 in West Palm Beach/Miami with 95 attendees, February 20 in Orlando with 32 attendees, and February 22 in Tampa with 27 attendees.<sup>602</sup> It also shows planned programs on March 6 in Marietta, GA with 100 anticipated attendees, and March 11 in Gainesville with 30 anticipated attendees.<sup>603</sup> The speakers listed for these programs include David Fishbain, Jennifer Strickland, David McGrew, Maribeth Kowalski, Bill Atkins, and Jackie LaPerriere.<sup>604</sup>

- B. A subsequent "Client Report" confirms the program in Marietta, GA went ahead with approximately 50 Publix pharmacists in attendance "representing stores in Georgia and South Carolina."<sup>605</sup> The report shows Purdue Medical Liaison Maribeth Kowalski presented for 2.5 hours on pain management and abuse/addiction issues including reviewing "the definitions of physical dependence, tolerance, addiction and psuedoaddiction [sic] (as defined and illustrated in the Greenwald slide kit),"<sup>606</sup> The "Greenwald slide kit" likely refers to a slide kit produced by Purdue titled "Opioids for Managing Patients with Chronic Pain: Community Pharmacists' Perspectives and Concerns...A Slide Kit Based on the Article by: Brian D. Greenwald, MD and Elizabeth J. Narcessian, MD Journal of Pain and Symptom Management 1999;17:369-375" from January 2001.<sup>607</sup> The Slide Kit was

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<sup>599</sup> PPLPC008000015224-PPLPC008000015225

<sup>600</sup> PPLPC025000014263-4264.

<sup>601</sup> PPLPC025000014263

<sup>602</sup> PPLPC008000014859

<sup>603</sup> *Id.*

<sup>604</sup> *Id.*

<sup>605</sup> PKY181887298 at -7328.

<sup>606</sup> PKY181887298 at -7328.

<sup>607</sup> PPLPC009000030950 (emphasis added)

replete with false and misleading information overstating the benefits of opioids and downplaying their risks, including the following:

- I. The slide kit includes a slide which defines pseudoaddiction as “an iatrogenic syndrome caused by inadequate pain management”<sup>608</sup> followed by a slide stating “The trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increase in the health consequences of opioid analgesic abuse.”<sup>609</sup>
  - II. The same slide kit, when identifying “disadvantages” of opioids, lists stigma of patients on prescription opioids for pain, regulation of opioids, and some minor side effects, without ever referencing the most important downsides of opioid use: addiction, dependence, and death.
  - III. Multiple slides describe pharmacists’ “resistance” to dispensing opioids, as if that were problematic, further contributing to the culture and climate of guiltting pharmacists into dispensing opioids against their better judgement and ignoring red flags for dispensing.
- C. A February 2001 email shows Paul D. Hines, Operations Director for Pharmacy at Publix, forwarding a Purdue press release to all Publix pharmacies and pharmacy supervisors.<sup>610</sup> The press release states, “Purdue Pharma is concerned about the diversion and abuse of OxyContin(R) Tablets in some regions of the country... News reports have frequently dwelt on the potential for addiction stemming from the abuse of OxyContin. Very often these reports create fear and reticence among physicians and patients who use this medication appropriately to achieve good pain control. When opioids are prescribed and used in accordance with the approved FDA labeling, they are safe and effective. OxyContin helps millions of people suffering from chronic pain return to normal, productive lives...”<sup>611</sup> In the email chain Seid reports, “This is the announcement sent out by Publix...It is our press release.

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<sup>608</sup> PPLPC009000030950 at \*33. See discussion of ‘pseudoaddiction’ at §C.4.n.

<sup>609</sup> PPLPC009000030950 at \*35. See discussion of the impacts of increased opioid prescribing and supply at §C.9-12.

<sup>610</sup> PDD1701091368 at -1369.

<sup>611</sup> *Id.*

A valuable byproduct of the Publix educational programs.”<sup>612</sup>  
 In a May 11, 2011 letter Stephen Seid thanks Richard Gourash for his “support of providing continued good pain management for appropriate patients. Publix was truly ahead of the curve by acting proactively with the pain management programs for pharmacists.”<sup>613</sup>

- D. Purdue emails show further collaboration with Publix on CE programs in 2003. An April 2003 email chain reports on additional meeting with Richard Gourash to discuss collaborating on 7-8 programs similar to those conducted on 2001.<sup>614</sup> A Purdue Medical Liaison Monthly Report for August 2003, confirms Maribeth Kowalski “provided two 3-hour continuing education programs to Publix Pharmacists in the Atlanta, Georgia area. The program “Assessment and Management of Pain: Continuum of Care” was held on August 22 and August 25, 2003 at the Publix Regional Office in Marietta, GA.<sup>615</sup> A slide deck from the program is rife with misleading statements about the safety and efficacy of prescription opioids when used in the treatment of pain.
- I. The CE slide deck highlights concerns about opioid regulations as “healthcare professional barriers to effective pain management.”<sup>616</sup> This is a curious statement since those regulations are in place to protect patient consumers from the well-documented harms of opioids, including the harms of addiction, dependence, and death. To suggest that opioid regulations are a barrier is to imply that dispensing pharmacists should ignore them. These regulations are further referenced as “restrictive regulations,”<sup>617</sup> again implying they are unfounded when in fact they originate from known risks of medicinal opioids dating back at least 100 years.
- II. The CE slide deck and speaker’s notes explicate physiologic dependence by giving multiple examples of dependence on non-opioid medications, like antihypertensive medications,<sup>618</sup> without explaining or

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<sup>612</sup> PDD1701091368

<sup>613</sup> 7003203614

<sup>614</sup> PPLPC031000131908 at -1909.

<sup>615</sup> PPLPC021000048039 (rows 639 and 644)

<sup>616</sup> PPLPC031000137304 (produced natively), at \*17.

<sup>617</sup> *Id.*, at \*18.

<sup>618</sup> *Id.*, at \*26



clarifying that opioid withdrawal and dependence is generally a more disabling syndrome with significant morbidity and mortality, including a common part of opioid addiction as a means of staving off withdrawal.

- III. The CE program makes a specious distinction between tolerance to opioids in people with addiction, whom the slide refers to as “addicts”, and tolerance in “patients with pain,” whom they notably identify as “patients”.<sup>619</sup> Tolerance is tolerance no matter who is exhibiting it. There is no difference in tolerance between patients with addiction and patients with pain. In both groups it means needing more of the substance over time to get the desired effect. By suggesting that tolerance is physiologically distinct in these groups, this CE program promotes the misleading message that patients with pain are somehow immune to the problems of dependence and addiction, of which tolerance is an important indicator. The distinction is extended by using a stigmatizing term for patients with addiction, namely “addicts”, and a normalizing, sympathetic term for people with pain, namely “patients”. Further, the slide deck makes the false claim that tolerance “rarely accounts for the need to significantly increase the dose.”<sup>620</sup> In fact, increasing the opioid dose is a common response to tolerance.
- IV. The CE slide deck uses the discredited term “pseudoaddiction” and describes it as “iatrogenic misinterpretation of relief-seeking behavior caused by undertreatment of pain.”<sup>621</sup> As detailed elsewhere in this Report, this conceptual framework for identifying drug-seeking behavior as relief-seeking for pain, encourages pharmacists to ignore a major red flag for the development of addiction.<sup>622</sup> Further, the statement that “behaviors cease when adequate pain relief is provided,”<sup>623</sup> ignores the fact that drug-seeking behavior in the case of addiction also ceases once more drugs are provided, and that in both cases the cessation is merely a temporary response that ends when the effect of the opioid dose wears off.

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<sup>619</sup> *Id.*, at \*28.

<sup>620</sup> *Id.*

<sup>621</sup> *Id.*, at \*29.

<sup>622</sup> See further discussion of ‘pseudoaddiction’ at §C.4.n.

<sup>623</sup> PPLPC031000137304 (produced natively), at \*29.

- V. The CE slide deck includes a phenomenon it calls “The Practitioner’s Dilemma”, which is described as the “therapeutic imperative” to “Always dispense opioid analgesics when they are appropriate for a patient,” and the “regulatory imperative” to “Never dispense opioid analgesics when they are inappropriate for a patient,” being equally important factors for pharmacists to balance.<sup>624</sup> In a subsequent 4 x 4 chart, it labels opioids dispensed for “legitimate pain patients” as a “good decision” and opioids dispensed for someone who is “not a legitimate pain patient” as a “bad decision.”<sup>625</sup> Both of these slides set up a false dichotomy between “always/never”, “legitimate/not legitimate”, and “good/bad”, when the reality is that “legitimate pain patients” can and do get addicted to opioids taken as prescribed by their doctors.
- VI. To support these misleading statements, the CE slide deck lists consensus statements from organizations that were funded by opioid manufacturers or whose guideline-authors were funded by opioid manufacturers, including the now-defunct APS.<sup>626</sup>
- VII. The CE slide deck includes the false statement: “Drug therapy is the cornerstone of treatment for the management of pain.”<sup>627</sup> This statement is false because no medication has reliably been shown to be the ‘cornerstone’ of treatment for chronic pain. It has long been known that chronic pain is a complex biopsychosocial disease which responds best to non-pharmacologic treatment. Further, a growing body of evidence shows that even the treatment of acute pain is not necessarily benefitted by opioids, which appear to work no better than non-opioid medications and incur more significant side effects. In fact, recent research shows that opioids are no better than placebo for acute pain.<sup>628</sup> Yet the CE makes the additional statement, “Non-pharmacologic interventions should not be used in

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<sup>624</sup> *Id.*, at \*30.

<sup>625</sup> *Id.*, at \*32.

<sup>626</sup> *Id.*, at \*34. See further discussion of professional medical societies at §C.4.k.

<sup>627</sup> *Id.*, at \*63.

<sup>628</sup> See *e.g.*, Jones CMP, *et al.* Opioid analgesia for acute low back pain and neck pain (the OPAL trial): A randomized placebo-controlled trial. *The Lancet*. 2023:1-9.

place of appropriate pharmacologic interventions but as an adjunct.”<sup>629</sup>

- VIII. The CE slide deck includes a slide on “Opioid Side Effects” which does not list opioid dependence or addiction, despite listing other side effects.<sup>630</sup>
- IX. Other misleading phrases in the slide deck include references to “no ceiling dose” for opioid therapy, “rescue doses,” and “breakthrough” pain.<sup>631</sup>
- X. The speaker notes state that “Addiction is reported to be rare with opioid use in properly managed pain patients. However, data are not available to establish the true incidence of addiction.”<sup>632</sup> In fact, there was and is overwhelming evidence that prescription opioids are addictive even when prescribed for pain and the incidence of addiction in the chronic pain population is well over the 1% promoted by the Pharmaceutical Opioid Industry.<sup>633</sup> A systematic review and meta-analysis from 38 studies shows that 8-12% of patients being prescribed opioids will develop an opioid addiction (opioid use disorder), and 21-29% will engage in misuse, making this a common rather than “rare” phenomenon.<sup>634</sup>
- XI. The programs were coordinated by Steve Bishop (National Accounts Manager) and were part of a tri-state educational initiative for the Publix grocery store chain.”<sup>635</sup> A January 2008 email references these CE programs, with Chris Sposato reporting on a positive interaction with a Publix district manager who attended a Purdue program, adding “I just wanted everyone to

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<sup>629</sup> *Id.*, at \*113.

<sup>630</sup> *Id.*, at \*110.

<sup>631</sup> *Id.*, at \*105, \*108-\*109. See further discussion of ‘breakthrough pain’ at §C.4.n. See additional discussion of ‘no ceiling dose’ at Appendix I.B.A.3.

<sup>632</sup> *Id.*, at \*110. I am aware that this language was approved by the FDA in 2005, however the language negotiated between Purdue and the FDA did not reflect scientific evidence of true addiction rates, as can be seen in the chart at §C.8.l.vi. In 2007, the statement regarding addiction being rare in pain patients was eliminated from the OxyContin label, a long-overdue change.

<sup>633</sup> See Timeline of Published Reports of Prescription Opioid Addiction 1979-2012 at §C.8.l.vi.

<sup>634</sup> Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*. 2015. doi:10.1097/01.j.pain.0000460357. See additional discussion of Vowles (2015) at §C.8.b.

<sup>635</sup> PPLPC012000064727 at 4743.

know that these programs from 4 years ago made a positive impression.”<sup>636</sup>

- vii. Rite Aid collaborated with Purdue to provide multiple “in-service” programs to pharmacists that promoted opioid use under the guise of “proper pain management education,” as detailed below.<sup>637</sup>
  - A. In April 2001, a series of emails between a Purdue sales rep, “Heather,” and her manager, “Sharlene,” described a Purdue in-service training session at the Rite-Aid Corporate Office with special attention to “John Boyle, Regional Pharmacy Development Manager,” whom the Purdue sales rep described as follows: “Our ROI [return on investment] will best be defined by John, whose regional coverage extends to over 120 stores in Northeast Philadelphia, North Philadelphia, Mt. Airy, Bucks County, and other outreaches within our district.”<sup>638</sup>
  - B. The Purdue sales rep went on to say, “This is of great importance because prior to this program, John and many other pharmacists had concerns with regulatory issues surrounding purchasing quantities of OxyContin and identifying appropriate patients. Now, John has made himself available as an advocate and is willing to assist in our efforts in proper pain management education.”<sup>639</sup>
  - C. The Purdue drug sales rep also stated, “I am personally pleased with the efforts put forth by myself regarding this program. As you know, Rite-Aid has presented numerous challenges to the Philadelphia Districts in the past. I believe that by creating the need for proper education, I have the opportunity to make significant progress with the key Rite-Aid pharmacies in my territory.”<sup>640</sup>
  - D. The “challenges” posed by the Philadelphia District can only mean that they weren’t dispensing, per Purdue, enough OxyContin. In a subsequent email, the Purdue sales representative wrote that the in-service training for Rite-Aid pharmacists “paid off,” in that Rite-Aid asked for similar training of 25 more of its pharmacists.<sup>641</sup> This email exchange

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<sup>636</sup> PPLPC024000273968 at 3969.

<sup>637</sup> PPLPC008000015973, at -5974.

<sup>638</sup> *Id.*

<sup>639</sup> *Id.*

<sup>640</sup> *Id.*

<sup>641</sup> *Id.*, at -5973.

depicts the ways in which Rite-Aid and Purdue Pharma collaborated to increase the supply of opioids.

- e. Purdue-sponsored CE programs for pharmacists contained misleading messages that were widely distributed to pharmacists nationwide, including to pharmacists practicing at Defendant Pharmacies. These misleading statements included statements about a purportedly low risk of addiction in chronic pain patients prescribed opioids, which we know to be false.
  - i. In 2001 and 2002, Purdue sponsored and promoted “Should I Dispense This?” continuing education programs to “educate” pharmacists, including presentations to hundreds of Walgreens, CVS, Walmart and Kroger pharmacists.<sup>642</sup> The presentations promoted the concept of “pseudoaddiction” and included a slide titled “The truth behind the fears: trends in opioid use and abuse” which stated that “the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid analgesic abuse”<sup>643</sup> citing as support a study written in 2000 by Joranson and others who were consultants and speakers for Purdue Pharma and Janssen Pharmaceuticals.<sup>644</sup>
  - ii. The Joranson (2000) article referenced above was refuted by its co-author Gilson in August 2004.<sup>645</sup> The 2004 Gilson reassessment of data from 1997-2002 stated, “Results demonstrated *marked increases in medical use and abuse of four of the five studied opioid analgesics. In 2002, opioid analgesics accounted for 9.85% of all drug abuse, up from 5.75% in 1997.* Increase in medical use of opioids is a general indicator of progress in providing pain relief. Increases in abuse of opioids is a growing public health problem and should be addressed by identifying the causes and sources of diversion, without interfering with legitimate medical practice and patient care.”<sup>646</sup> Notably, the number of drug abuse incidents is a reflection of hospitalization incidents, as demonstrated by Gilson’s description of the DAWN data set: “*Drug Abuse Warning Network: DAWN is a national surveillance system, begun in 1972, that reports data annually on drug-related visits to a*

<sup>642</sup> PPLPC022000019177; PPLPC022000019178; PPLPC036000008325 and PPLPC008000038150.

<sup>643</sup> PPLPC022000019178 (produced natively), at \*38; PPLPC022000019179 (produced natively), at \*36.

<sup>644</sup> Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710-1714, at p. 1710. Joranson and Dahl are also discussed at above at §C.4.I., and below at Appendix II. The article cites the following conflicts of interest: “Financial Disclosures: Mr Joranson receives honoraria from Knoll Pharmaceutical, Purdue Pharma, and Janssen Pharmaceutical. He also receives unrestricted grants from Knoll Pharmaceutical and Purdue Pharma and is a consultant for Purdue Pharma. Dr Dahl serves on the Speakers Bureau for Purdue Pharma and is a consultant for Knoll Pharmaceuticals.”

<sup>645</sup> Gilson AM, Ryan KM, Joranson DE, Dahl JI. A Reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control. *J Pain Symptom Manage*. 2004;28:176-188.

<sup>646</sup> *Id.* at p. 176. (emphasis added)

national probability sample of hospital EDs located throughout the coterminous United States. It is a large-scale ongoing retrospective survey of medical records that provides information about the health consequences of drug abuse that result in visits to hospital EDs.”<sup>647</sup> Despite that the authors were part of the industry-sponsored Wisconsin Pain and Policy Studies Group, hence the mixed message about legitimate pain patients the article nevertheless provided clear public notice of the growing harms, including increased hospitalizations, resulting from expanded prescription opioid use. I am not aware of any evidence that Walgreens, CVS, Walmart or Kroger ever corrected the misinformation that was presented to their pharmacists through their collaboration with Purdue.

- iii. Also in 2001 and 2002, Purdue sponsored continuing education programs titled “Pain Management for Pharmacists,”<sup>648</sup> including presentations to hundreds of Walgreens, Walmart, Rite-Aid, CVS and Kroger pharmacists nationwide.<sup>649</sup> These presentations also promoted the concept of “pseudoaddiction.”<sup>650</sup> Further, the 2001 presentation included the statement that “risk of addiction is rare in patients with no history of addiction who are prescribed opioids for the management of pain”<sup>651</sup> and the 2002 presentation included the statement that “de novo addiction is reported to be rare when they [patients] are treated with opioids.”<sup>652</sup> As discussed elsewhere in this report, addiction is *not* rare among chronic pain patients taking opioids and some 10-30% of chronic pain patients on long-term opioid therapy are addicted to opioids.
- iv. These Purdue sponsored continuing education materials provided misinformation to pharmacists concerning the false assertions of the low risk and great benefits of opioids, with Pharmacy Defendants enthusiastic cooperation. Some of these materials also included a multiple choice test at the end of the class which emphasized the misleading messages about opioids for pharmacists.<sup>653</sup> Later emails endorsed these programs, with one Purdue sales executive noting that “The absolute last thing we want is for the OxyContin prescription to

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<sup>647</sup> *Id.* at p. 177.

<sup>648</sup> PPLPC022000013223; PPLPC031000098402

<sup>649</sup> PPLPC008000038150

<sup>650</sup> PPLPC022000013223, at \*22; PPLPC031000098402, at \*12 speaker notes.

<sup>651</sup> PPLPC022000013223, at \*33.

<sup>652</sup> PPLPC031000098402, at \*12 speaker notes.

<sup>653</sup> *See, e.g.*, PPLPC024000044089 at -4090.

be bounced out at the pharmacy level because of unfounded fears from the ‘uneducated’ pharmacist.”<sup>654</sup>

- f. Pharmacy Defendants collaborated with pro-opioid industry advocacy and lobbying organizations.
  - i. A June 2001 letter to CVS pharmacists announced CVS’ participation in *Partners Against Pain*, sponsored by Purdue Pharma. The letter called Purdue “a leader in educating the healthcare community on effective pain management and the appropriate use of pain medicines.”<sup>655</sup> Purdue’s *Partners Against Pain* campaign used the same promotional tactics and misleading messages that Purdue has pleaded guilty to in federal court, including overstating the benefits and understating the risks of opioids prescribed for pain.
    - A. A nearly identical June 2001 letter to Walgreens pharmacists, on Walgreens letterhead and signed by Dr. Robert F. Reder, Purdue VP, Medical Affairs & World Drug Safety, announced Walgreens’ participation in *Partners Against Pain*, sponsored by Purdue Pharma. The letter encouraged Walgreens pharmacists to visit [www.partnersagainstpain.com](http://www.partnersagainstpain.com) which according to the letter “provides pain information, assessment tools, and support.”<sup>656</sup> Further, the letter encouraged Walgreens’ pharmacists to direct patient customers to the website as well.<sup>657</sup>
    - B. An excerpt from the *Partners Against Pain* website from March 2001, under the subheading “Barriers to Effective Cancer Pain Management: A Review of the Literature,” included the following: “The majority of physicians and nurses .... fear that opioid use will result in addiction, drug tolerance, and uncontrollable side effects, especially respiratory depression. They fail to differentiate between addiction and physical dependence and to recognize that a) the risk for addiction is low in patients with no history of substance abuse and b) that there is little or no tolerance to the analgesic effects of opioids. They often base opioid doses on the severity of disease or their own fear of drug tolerance rather than on the intensity and level of the patient’s pain. Many do not acknowledge the efficacy of opioids administered orally or

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<sup>654</sup> PPLPC029000019201 at -9201.

<sup>655</sup> PDD1501726314

<sup>656</sup> PDD1501724898. *See also* PDD1501726314 (CVS).

<sup>657</sup> *Id.*



antidepressants prescribed as adjuvants.”<sup>658</sup> This statement encapsulates many of the false and misleading messages about opioids promulgated by the Industry.

- C. In fact, the risk of addiction to opioid analgesics prescribed to a doctor is high. Tolerance to the analgesic effects of opioids is common and probably occurs in the majority of consumers. A patient’s subjective endorsement of pain should never be the sole criterion on which opioids are titrated, because dependent patients frequently cannot distinguish between the pain of opioid withdrawal and the pain of whatever condition led them to initiate opioid therapy in the first place.
- D. Although the earliest date in the documents that I have seen linking CVS and Walgreens to the *Partners Against Pain* program is April and June 2001 respectively,<sup>659</sup> the content of the material on the *Partners Against Pain* website after 2001 was similar to Purdue’s earlier misrepresentations, including invalid terms such as “pseudoaddiction” and “pseudotolerance.” The website repeatedly promoted the now discredited JCAHO mandates for “regular assessment of pain and the establishment of policies and procedures that support the appropriate use of pain medication” along with “educational materials developed by Purdue Pharma to help you comply with the JCAHO pain standards.”<sup>660</sup>
- E. Purdue’s Executive Director of National Accounts and Trade Relations, Stephen Seid, testified regarding the June 2001 CVS/Purdue *Partners Against Pain* (PAP) letter.<sup>661</sup> “First of all, as I remember, the letter was prepared – [CVS] agreed to do this, but the letter was prepared by [CVS]. It got reviewed, but it was their letter since it was on their letterhead....So the goal was to build a better relationship with CVS, No.1”<sup>662</sup> The letter was probably sent to “about 12,000 pharmacists and about 18,000 pharmacy techs.”<sup>663</sup>

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<sup>658</sup> Partners Against Pain website (March 2001), [https://web.archive.org/web/20010605165846/http://www.partnersagainstpain.com/html/profed/pmc/pe\\_pmc4.htm#barriers](https://web.archive.org/web/20010605165846/http://www.partnersagainstpain.com/html/profed/pmc/pe_pmc4.htm#barriers) (last accessed December 14, 2020)

<sup>659</sup> See e.g., PKY180409814 and PPLPC012000040664 (produced natively), at \*56

<sup>660</sup> Partners Against Pain website (June 2004), <https://web.archive.org/web/20040603003006/http://partnersagainstpain.com/index-mp.aspx?sid=7> and <https://web.archive.org/web/20040611091507/http://partnersagainstpain.com/index-hs.aspx?sid=22&aid=7795>

<sup>661</sup> PDD1501726314; See also, PPLPC008000018733 (produced natively), at \*46

<sup>662</sup> Deposition of Stephen Seid (December 12, 2018), 119:19-120:11.

<sup>663</sup> *Id.*

- ii. Pharmacy Defendants joined together with the The National Association of Chain Drug Stores (NACDS) and the Pain Care Forum (PCF), “a loose coalition of drugmakers, trade groups and dozens of nonprofits supported by industry funding,”<sup>664</sup> to disseminate pro-opioid messages, even amidst a growing opioid epidemic. Between 2006 and 2015 the PCF spent more than \$880 million on campaign contributions and lobbying expenses to promote their opioid agenda, including millions of dollars for state-wide candidates in Ohio, Georgia, North Carolina and Texas.<sup>665</sup>
  - A. The NACDS/PCF opioid agenda included shifting media coverage away from the opioid epidemic to focus instead on maintaining access to opioids. “As you may recall, NACDS spearheads the communications working group of the Pain Care Forum. As a group we have been working to tell the story in the media of the unintended consequences that legitimate patients face when they cannot access prescription drug medications. Often times, the media focus just on abuse in their coverage.”<sup>666</sup>
  - B. The NACDS/PCF efforts included developing a “microsite” on Drug Store News featuring interviews with patient advocates.<sup>667</sup> These interviews included false and misleading pro-opioid messages about opioid misuse and addiction.<sup>668</sup>
  - C. According to an October 2014 article titled “The Other Side of the Pain Medication Debate-Legitimate Patients” and still active on the NACDS website, the purpose of the microsite was to “help bring attention and reduce the stigma Americans who live with chronic pain often experience. The site puts a face on these legitimate patients and what it means when they are unable to access the medications they need to manage pain...heightened awareness in the media about the often untold side of the prescription drug abuse story is an important advancement that highlights the unintended victims of the debate - patients who legitimately need medications.”<sup>669</sup> This

<sup>664</sup> Matthew Perrone, Ben Wieder, “Pro-Painkiller Echo Chamber Shaped Policy Amid Drug Epidemic” Public Integrity (Dec. 15, 2016), *see* <https://publicintegrity.org/politics/state-politics/pro-painkiller-echo-chamber-shaped-policy-amid-drug-epidemic/>.

<sup>665</sup> Associated Press and the Center for Public Integrity, Politics of Pain: A decade of opioid lobbying (2016), [http://data.ap.org/projects/2016/cpi\\_ap\\_opioids/indexcpiap.html](http://data.ap.org/projects/2016/cpi_ap_opioids/indexcpiap.html)

<sup>666</sup> WAGMDL00590913, at -0917.

<sup>667</sup> *Id.*, at -0916.

<sup>668</sup> Microsite archived at: <http://web.archive.org/web/20140712213014/http://www.drugstorenews.com/pain-management-2>

<sup>669</sup> Lisa Boylan, *The Other Side of the Pain Medication Debate: Legitimate patients*. NACDS.org, Oct. 2, 2014 (last accessed January 28, 2021). *See*: <https://www.nacds.org/news/the-other-side-of-the-pain-medication-debatelegitimate-patients/>

messaging created a false dichotomy between “legitimate pain patients” and those who become addicted to prescription opioids, when in fact they are all too often one and the same. As noted at Section §C.8 of this report, approximately 21-29% of patients taking opioids “legitimately” prescribed by their physicians for chronic pain have an opioid use disorder.

- D. Other NACDS/PCF statements include: (i) “But the media focus has historically been on the addicts and how to curtail their access to the pain medicines they crave. That creates a real stigma that inhibits access for legitimate patients from doctors to pharmacists to the patients themselves;”<sup>670</sup> and (ii) “[w]hile the number of patients who have a legitimate need for prescription painkillers — 100 million plus — is vastly more than the number of people addicted to painkillers — 11 million — there is a stigma attached to the prescribing, dispensing and utilization of pain medicines. And that stigma has created an, [sic] at times, insurmountable hurdle that leaves legitimate patients suffering in silence.”<sup>671</sup> Invoking the Institutes of Medicine statistic regarding the prevalence of pain in the United States — 100 million, falsely conveys that every American with pain needs opioids. In fact, far fewer than the 100 million Americans cited in the IOM report have pain severe enough to warrant any medical intervention; and among those who do, opioids are appropriate for only a very small minority.<sup>672</sup>
- E. An NACDS representative wrote in an email in 2013, “With respect to DEA, last year the NACDS Board directed us to convene a Task Force to develop policies and a strategy to push back on DEA’s aggressive tactics including expecting pharmacies to be policemen.”<sup>673</sup> Pharmacies, acted through the NACDS Board that directed such a Task Force be convened.

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<sup>670</sup> Michael Johnsen, *Chronic Pain Sufferers Advocate Against Sigma of Prescription Pain Meds*, May 29, 2014 (last accessed January 28, 2021). See:

<http://web.archive.org/web/20140703054325/http://www.drugstorenews.com/article/chronic-pain-sufferers-advocate-against-stigma-prescription-pain-meds>

<sup>671</sup> *Id.*

<sup>672</sup> See Appendix IV to this report, citing a recent NIH study reporting that “High Impact Chronic Pain,” defined as the experience of pain on most days over the past 3 months, with concomitant limitations on activities due to pain, is experienced by 4.8% of US adults, or about 10.6 million people—about 1/10<sup>th</sup> of the “100 million” figure erroneously relied on by defendants to exaggerate the need for opioid pain treatment.

<sup>673</sup> Rite\_Aid\_OMDL\_0027468

- F. The NACDS also made it part of their mission to “draft a letter to the Hill” regarding hydrocodone scheduling.<sup>674</sup> For nearly a decade the Department of Justice advocated up-scheduling hydrocodone products from Schedule III to Schedule II, providing an additional layer of protection against misuse and diversion. Instead of supporting this initiative, which was ultimately approved, pharmacies working with NACDS and the PCF lobbied against it. “We are also working with the patient groups to advocate that FDA not recommend rescheduling these products.”<sup>675</sup>
- G. Pharmacies’ efforts against rescheduling hydrocodone provide another example of their contribution to the problems of opioid oversupply, misuse, addiction, and death, and their failure to work with other regulatory agencies to stem the tide of the opioid epidemic.
- iii. NACDS, whose members include Defendant Pharmacies Kroger and Publix as well as opioid manufacturers and distributors<sup>676</sup> disseminated misleading messages to pharmacists about the safety and efficacy of opioids, including misleading messages sponsored by opioid manufacturers.
  - A. Beginning in 1997, NACDS published and distributed a periodic newsletter, “The Practice Memo,” to approximately 114,000 chain pharmacists, 134,000 community pharmacists and 100 schools and colleges of pharmacy.<sup>677</sup>
  - B. One example of the Practice Memo, from September 2002, misleadingly stated that “appropriate prescription medication use rarely leads to addiction” and cited to Porter & Jick.<sup>678</sup> The Practice Memo also encouraged pharmacists to recommend that doctors write prescriptions for “more potent medication” for ‘breakthrough’ pain and sought to normalize high dosage opioid prescribing for chronic pain, stating that

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<sup>674</sup> *Id.*

<sup>675</sup> *Id.*

<sup>676</sup> NACDS Elects 2021-2022 Officers, New Members to Board and Executive Committee (April 28, 2021). *See also*: NACDS Foundation Welcomes Seven First-Time Members to Board of Directors (April 26, 2022) <https://www.nacds.org/news/nacds-elects-2021-2022-officers-new-members-to-board-and-executive-committee/> and <https://www.nacds.org/news/nacds-foundation-welcomes-seven-first-time-members-to-board-of-directors/>. *See also*: NACDS names 2022-23 officers, directors at <https://www.supermarketnews.com/executive-changes/nacds-names-2022-23-officers-directors> and <https://www.nacds.org/news/mark-panzer-of-albertsons-companies-cites-power-of-nacds-to-help-chains-suppliers-listen-learn-and-engage-for-success/>

<sup>677</sup> JAN-MS-01125392

<sup>678</sup> PKY181291507, at -1508

“Controlling chronic, severe pain may often require using much higher doses of pain medication...it is not uncommon for patients in severe pain to use more than 90mg every four hours.”<sup>679</sup> As discussed elsewhere in this report, serious and certain risks associated with long-term opioid therapy increase with increasing dose and duration.

- C. The September 2002 Practice Memo also stated that “The most common types of chronic pain include migraine headaches, low back pain, cancer pain, and arthritis pain”<sup>680</sup> without acknowledging that there has never been any reliable evidence that opioids are effective for expanded uses such as migraine, low back pain, or arthritis. See §C.7, below (No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain).
- D. Further, the September 2002 Practice Memo stated that “Not only do pharmacists have responsibility to ensure correct use of medications, they must also ensure that their patients are receiving adequate therapy. Many patients in chronic pain suffer needlessly because doctors and pharmacists are overly concerned about addiction and ‘forget’ to focus on treating the patient and improving the patient’s quality of life, a syndrome commonly referred to as ‘opiophobia.’”<sup>681</sup> This is an example of professional shaming around ‘undertreatment of pain’ which was a powerful mechanism by which pharmacists were pressured to dispense opioids.
- E. The November 2008 edition of the Practice Memo, distributed to hundreds of thousands of pharmacists was sponsored by opioid manufacturer Ortho-McNeil-Janssen.<sup>682</sup> Ortho-McNeil-Janssen paid \$60,000 to sponsor the newsletter.<sup>683</sup>
- F. The November 2008 Practice Memo cited to a Purdue-sponsored study by KOL Russell Portenoy<sup>684</sup> to state that: “While the perception of addiction and misuse is high among patients receiving opioids, the reality is different. In a 3-year registry study of non-cancer patients requiring opioid

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<sup>679</sup> *Id.*

<sup>680</sup> *Id.*

<sup>681</sup> *Id.* (emphasis in original)

<sup>682</sup> JAN-MS-00477197

<sup>683</sup> JAN-MS-01125392

<sup>684</sup> Portenoy R, *et al.* Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007;23:287-299. DOI: 10.1097/01.brs.0000186860.23078.a8.

analgesia for moderate to severe pain, only six cases (2.6%) of possible drug misuse were reported” and that the risk of patient addiction was “much smaller than commonly believed.”<sup>685</sup> As discussed elsewhere in this report,<sup>686</sup> there are numerous flaws in Portenoy’s study, which made it an unreliable indicator of the true risk of addiction to prescription opioids, including but not limited to (a) the study excluded patients with self-reported past or present substance or alcohol abuse, which is atypical of real-world populations of prescription opioid patients; (b) the claim of a 2.6% rate of problematic use was based on an inappropriate denominator consisting of the entire population of 233 patients that started the study, without accounting for the 127 (>50%) of patients who dropped out of the study or were terminated by Purdue, the study sponsor; (3) the average daily dose was 52.5 mg of oxycodone (or 78.75 MME), which is lower than many real-world patients received, and the risk of addiction increases with higher dose; (4) 76% of the study participants had demonstrated prior acceptance of opioid therapy by participation in previous studies, which would not be true in a real-world patient population; and (5) many other prior and contemporaneous studies had shown far higher rates of addiction (up to 35%), but the Purdue-sponsored CE presentation to the pharmacists made no mention of those important data.<sup>687</sup>

- iv. Defendant Rite Aid Pharmacy collaborated with the APF to create a patient-facing educational pamphlet on pain. In the pamphlet itself, Rite Aid described its collaboration with the APF as follows: “As Rite Aid continues its mission of ensuring that customers receive the kind of information and services that really make a difference, the American Pain Foundation has been an invaluable resource.”<sup>688</sup> The pamphlet itself perpetuates opioid-promoting messages which are not supported by the science.

- A. The pamphlet claims “If you act quickly when pain starts, you can often prevent it from getting worse. Take your

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<sup>685</sup> JAN-MS-00477197, at -7198.

<sup>686</sup> See §C.8.m., §C.8.p. and Appendix I.C. for further discussion of Portenoy (2007).

<sup>687</sup> Portenoy, “Long Term Use of Controlled-release Oxycodone”, fn. 684, above, at Figure 1 and p. 291.

<sup>688</sup> PAIN RELIEF GUIDE: Tips and advice from your pharmacist. Rite Aid Pharmacy.

<https://docplayer.net/12194913-Pain-relief-guide-tips-and-advice-from-your-pharmacist.html> ; See Perrone, M. Pro-painkiller echo chamber shaped policy amid drug epidemic. September 19, 2016 Updated — December 15, 2016 at 9:09 am ET. [publicintegrity.org/politics/state-politics/pro-painkiller-echo-chamber-shaped-policy-amid-drug-epidemic/](http://publicintegrity.org/politics/state-politics/pro-painkiller-echo-chamber-shaped-policy-amid-drug-epidemic/)

medications when you first experience pain. If your pain does get worse, talk to your healthcare provider. Your provider may safely prescribe higher doses or change the prescription.”<sup>689</sup> These statements are echoes of the same misleading messages promoted by the Pharmaceutical Opioid Industry regarding the ‘wind-up’ phenomenon, encouraging patients to take opioids early and often as a way to reduce future pain. Instead, this kind of messaging promotes increased opioid consumption leading to tolerance and dependence, necessitating further prescribing. As for prescribing “higher doses”, this too is an echo of the misleading marketing around “no ceiling dose” which the Pharmaceutical Opioid Industry disseminated to promote sales. In contrast to these misleading promotional messages, the evidence shows that the higher the dose of opioids, the higher the morbidity and mortality.

- B. The discussion of opioid risks in the pamphlet is seriously misleading in that it omits mention of the risk of overdose or death with opioids.<sup>690</sup> Tolerance, physical dependence and addiction are defined, but the extent of the risk of those effects is not mentioned. The pamphlet erroneously states that constipation is “the side effect that is most difficult to manage.”<sup>691</sup> To the contrary, addiction is at least as complex to manage as constipation, and far more dangerous.
- C. The pamphlet encourages the use of the unvalidated pain “scale from 0 to 10.”<sup>692</sup> Further, the pamphlet claims that opioids are “very effective in treating pain”<sup>693</sup> without distinguishing the evidence for acute pain (which is robust) from the evidence for chronic pain (which is weak and unreliable).
- D. The pamphlet describes physical dependence as “normal and does not mean you are addicted,”<sup>694</sup> when in fact addiction and dependence are closely linked and dependence alone is a debilitating and hard-to-treat condition.
- E. Finally, the pamphlet states “Some medications used to relax muscles, or treat insomnia or anxiety may be used in the overall management of pain.”<sup>695</sup> This statement lacks

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<sup>689</sup> *Id.*

<sup>690</sup> *Id.*, at p. 9.

<sup>691</sup> *Id.*, at p. 3.

<sup>692</sup> *Id.*, at p. 4.

<sup>693</sup> *Id.*, at p. 9.

<sup>694</sup> *Id.*

<sup>695</sup> *Id.*



foundation, and seems to promote the use of benzodiazepines and muscle relaxants, which when used in combination with opioids are known to increase risk of accidental overdose and such combination use is a “red flag” for diversion as discussed in the following section of this report.

- g. Walgreens, in collaboration with Purdue, built stores where prescription opioids were readily available and abundant, sometimes called “Super Stores,” to enhance unrestricted flow of opioid pain pills
  - i. Walgreens has claimed that because it dispenses medications in response to a doctor’s prescription, it is merely passive purveyors of opioid pain pills. But in fact, Walgreens played a pivotal role in driving demand. As the only entities that had direct contact with both prescribing doctors and patient consumers, pharmacies provided a critical link in the corporate supply chain and used this role to promote the supply of prescription opioids, and thereby substantially contributed to the opioid epidemic. As explained below, Purdue collaborated with Walgreens as part of its overall method of assuring widespread availability and access to its opioid products.
  - ii. A series of February 1997 internal Purdue emails regarding Walgreens pharmacy calls began with Purdue Sales rep Eric Perham writing to his colleague/manager: “Today was a great day for pharmacy calls!”<sup>696</sup> The email then goes on to describe Perham’s conversation with Walgreens pharmacist Bob Brody.
  - iii. Walgreens pharmacist Brody’s protocol recommendations included “the 24 hour stores increase there [sic] narcotic inventory as much as 8 fold to cover each area,” informing “high prescribers in the area that those stores will always have an adequate inventory,” that “These stores will also have well informed pharmacist in the area of pain management” to “eliminate any confusions [sic] on the ‘correct’ dose for the patient,” and finally, that these select, well-stocked pharmacies will have the added benefit that they will “save patients time from having to shop around for stores that carry the pain medications. *The doctors will have the assurance that the pain meds will be filled by a pharmacist less likely to question his/her prescribing habits.*”<sup>697</sup>
  - iv. The summary depicts the Walgreens pharmacist, Brody, as actively involved in not just promoting opioids but specifically OxyContin through development of a “‘simple’ pain management protocol at the

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<sup>696</sup> PDD8801156563 at -6564.

<sup>697</sup> *Id.* at -6564-6565. (emphasis added)

pharmacy level”, including making sure that pharmacies always have OxyContin in stock, and discouraging pharmacists from questioning opioid prescriptions, denying them their critical role as safeguards against misuse and diversion.<sup>698</sup>

- v. The Purdue sales manager Chris Sposalto responded to these suggestions with, “Great cccntact [sic]!!...While we are not in the business of promoting pharmacies per se, it is our obligation to our customers to direct them to locations that will (without a doubt) be carrying our OxyContin line. You should inform these key Dr’s, nurses, PA’s, NP’s, etc on your calls and have a list available near their phones so they can take action toward OxyContin prescriptions at a moment’s notice.”<sup>699</sup>
- vi. According to a November 1999 Purdue memorandum, Bob Brody’s planned protocol to promote OxyContin was successfully implemented by Walgreens.<sup>700</sup> The memorandum summarized continuing education-accredited presentations to pharmacists and stated that “One of the Walgreen’s pharmacists (Bob Brody) got up at the beginning of each meeting and made a short presentation on his store and a program that they have implemented. His store actively advertises to area MDs and patients that they are a ‘full-service’ pain management pharmacy. This service includes providing a list to the physicians’ offices of all CIIIs they have in stock (and they have everything), accepting ‘verbal orders’ for Class II analgesics prior to presentation of the original prescription at the store to decrease ‘waiting time’, allowing partial fills on CII prescription in terminal patients, and accepting after hours ‘emergency CII prescriptions’ without a hassle. This pharmacist was fantastic.”<sup>701</sup>
- vii. In a series of May 1997 emails to Purdue’s Chesapeake District sales force, with the subject heading “OxyContin Super Stores!!”<sup>702</sup> Purdue executives incentivized and coached sales representatives on how to create OxyContin Super Stores, the “pill mill” equivalent of chain pharmacies. Purdue’s actions capitalized on the pivotal role that pharmacies and pharmacists played in promoting OxyContin.
- viii. First, Purdue incentivized drug representatives to create OxyContin Super Stores by promising them a trip to London and a bonus: “OxyContin 80mg is your ticket to London. OxyContin 80mg is your ticket to bonus. OxyContin 80mg is crucial to your success. But, only if

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<sup>698</sup> *Id.* at -6564-6565.

<sup>699</sup> *Id.* at -6563-6564.

<sup>700</sup> PPLPC028000008080, at -8081.

<sup>701</sup> *Id.*

<sup>702</sup> PPLPC024000002380

your doctors' patients can GET it!"<sup>703</sup> In other words, make sure the pharmacies, including Walgreens, are stocked with OxyContin.

- ix. Among the "important notes" for Purdue sales reps was the following: "Call in this Friday morning with the number of 40 & 80mg stores you have stocked this week," and "Set up Super stores: Every territory must have a MINIMUM of eight to twelve SUPER STORES identified and stocked."<sup>704</sup>
- x. Purdue also offered "how to" advice to its sales reps, such as: "Ask your key doctors, nurses, clinics and hospices about specific patients on doses of more than one 40mg tablet q12h. Get them to switch the patients to 80mg tablets. Create the demand. Recognize the need. Arm yourself with this information. Use it to convince your pharmacies.... How many tablets are your 80mg patients taking? Some are taking 8 tablets!! You'll lose that patient on the next titration."<sup>705</sup>
- xi. Especially noteworthy here is the statement "Create the demand," as it highlights the fact that opioid manufacturers sought the assistance of pharmacists and pharmacies to influence the numbers and types of prescriptions that were written.
- xii. In an email from Thomas Mollick, Sunshine District Manager, for Purdue, to Tony Goodman, Group Product Manager/Analgesics, dated June 12, 2001, Mollick wrote: "Port St. Lucie, FL is an identified top 10 hot spot for abuse and diversion. I contacted the DM at Walgreen's in this area, Richard Ashworth, because of inadequate stocking of OxyContin in this area. He informed me that a few pharmacists were afraid to stock and dispense OxyContin because of theft. He also informed me that OxyContin is one of the most highly profitable items to dispense and did not want to miss out on any sales because of fear of theft or suspicion of diversion."<sup>706</sup>
- xiii. Despite this pharmacy district being identified as a hot spot for abuse and diversion, and despite pharmacists' fear of stocking OxyContin because of theft, this Walgreens' district manager reached out to Purdue to ensure OxyContin supply and not miss out on these "highly profitable items."<sup>707</sup>

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<sup>703</sup> *Id.*

<sup>704</sup> *Id.*

<sup>705</sup> *Id.* at -2381.

<sup>706</sup> PPLPC024000044089, at -4090.

<sup>707</sup> *Id.*

- xiv. In 2008, Walgreens had an agreement with Purdue wherein Purdue agreed to replace OxyContin losses at a pharmacy due to theft or robbery.<sup>708</sup> Theft and robbery from pharmacies are a form of diversion. Replacing opioid pharmacy stock without increasing safeguards to mitigate diversion, does little to help the public good.
- xv. March 2008 internal Purdue emails described a potential meeting with the “Big 3” distributors “to talk about DEA’s latest plans to squeeze the wholesalers and distributors on ‘pain clinics’... We really do have to partner with our own customers to help them in their business with pharmacies catering to ‘pain clinics’. Otherwise, they will cut them off based on some kind of threshold.”<sup>709</sup> This email makes it clear that Purdue understood the importance of pharmacies catering to pain clinics as essential to their profit margin.
- xvi. A July 2013 Purdue presentation on order monitoring and retailer due diligence included a reference to meetings with major pharmacies: “senior management at Walgreens, Rite Aid, Walmart.”<sup>710</sup> After a summary of recent DEA actions against pharmacies related to diversion, Purdue detailed the “ORDER MONITORING IMPACT: Possible reduction/limitation of supply.”<sup>711</sup> Among the actions Purdue proposed was working “on a study to utilize with the trade on what an appropriate patient ‘looks like’”<sup>712</sup> and “Enhanced pharmacist education” including “Broad distribution of the OxyContin Pharmacist Guide.”<sup>713</sup> Purdue concluded that “inventory across supply chain [was] decreasing.”<sup>714</sup> Purdue was “hearing of overflow into stores who have inventory causing them to run out early and unable to obtain more product before the next months and next ‘allotment.’”<sup>715</sup>
- xvii. This document and the ones that follow highlight the regular communications between Purdue and pharmacy executives, demonstrating that corporate leaders at all levels of the supply chain were aware of the risks associated with OxyContin diversion.
- xviii. In a spreadsheet memorializing discussions between Purdue executives and Walgreens pharmacy supervisors in April 2012 regarding Butrans and OxyContin, Purdue executives documented that “the main

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<sup>708</sup> PPLPC004000170570, at -0572.

<sup>709</sup> PPLPC018000200323-0324

<sup>710</sup> PPLPC004000363085 (produced natively), at \*14.

<sup>711</sup> *Id.* at \*2-6 and \*9.

<sup>712</sup> *Id.* at \*19.

<sup>713</sup> *Id.* at \*20.

<sup>714</sup> *Id.* at \*21.

<sup>715</sup> *Id.*

takeaway was that they said we have ‘open line of communication’ to them with ANY stocking issues (for any of our products) in any of their stores. They were very supportive.”<sup>716</sup>

- xix. An email dated January 20, 2017 summarizing Purdue’s ‘Weekly Highlights P/E’ included a summary provided by Tony Scifo, Purdue’s National Account Executive, regarding a meeting with Gina Telford of Purdue and two Walgreens HCSs [Health Care Supervisors], Andy Davenport and Eleanor Wong. Andy Davenport had responsibility for 66 Walgreens stores and approximately 175 Walgreens pharmacists ; Eleanor Wong had responsibility for 49 Walgreens stores and approximately 125 Walgreens pharmacists.<sup>717</sup> Significant aspects of this meeting include the following:
  - A. “Walgreens was [Purdue’s] largest account in 2016 up 3.6%.”<sup>718</sup>
  - B. “Discussed current patient co-pay cards and Managed Care coverage. Gina discussed the National patient savings cards and the Hysingla card for California.”<sup>719</sup>
  - C. Discussed Walgreens internally posting Purdue managed care coverage and savings cards.<sup>720</sup>
  - D. Discussed objective “to solidify an open line of communication between Gina and the Walgreens DMB’s [District Business Managers] when appropriate patients for whatever reason do not have their scripts filled. Both Andy and Eleanor were open to Gina contacting them.”<sup>721</sup>
  - E. “Andy and Eleanor were impressed by the store volume as well as the total volume in California of \$28 million.”<sup>722</sup>
- xx. Walgreens’ active collaboration with Purdue is manifest by the remarkable sales of OxyContin at Walgreens pharmacies: “Walgreens distributes ~\$374M (16.8%) of Purdue’s prescription products;

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<sup>716</sup> PPLPC004000323637, PPLPC004000323638

<sup>717</sup> PPLPC018001400813, at -0826.

<sup>718</sup> *Id.*

<sup>719</sup> *Id.*

<sup>720</sup> *Id.*

<sup>721</sup> *Id.*, at -0826-0827.

<sup>722</sup> *Id.*

Walgreens is the largest of the >200 retail chains that dispense Purdue Rx Products.”<sup>723</sup>

- xxi. In 2008, Walgreens was “the number 1 redemption [sic] of OxyContin Savings Cards in the United States.”<sup>724</sup>
- xxii. Purdue urged Walgreens to further expand the Butrans and OxyContin savings programs with an additional e-voucher program, suggesting a potential 2012 financial upside to Walgreens of \$27 million and a 5% market share increase for Butrans and “new to brand” OxyContin customers.<sup>725</sup> In October 2013, Walgreens executed an e-voucher agreement for Purdue’s controlled substance products, including OxyContin and Butrans.<sup>726</sup>
- xxiii. Below is a chart showing the average monthly and annualized OxyContin sales at Walgreens from 2010 to 2017. OxyContin sales in 2010 continued to be at very high levels through 2017.<sup>727</sup>

OxyContin				
Year	Avg. Monthly	Annualized	Annual Change	% Change
2010	\$25,269,202	\$303,230,419		
2011	\$33,828,465	\$405,941,577	\$102,711,158	33.9%
2012	\$34,247,556	\$410,970,670	\$5,029,093	1.2%
2013	\$28,203,503	\$338,442,039	(\$72,528,630)	-17.6%
2014	\$26,663,383	\$319,960,601	(\$18,481,439)	-5.5%
2015	\$27,760,433	\$333,125,200	\$13,164,599	4.1%
2016	\$27,714,597	\$332,575,162	(\$50,038)	-0.2%
2017	\$25,157,465	\$301,889,576	(\$30,685,586)	-9.2%

- xxiv. These documents attest to Walgreens’ role in assuring the widespread availability of opioids, and in promoting the specific product, OxyContin.
- xxv. An April 27, 2001 Purdue memo summarized a meeting between Purdue’s Senior Director of National Accounts and Trade Relations, Stephen Seid, and Sheila Bennett, Walgreen’s Category Manager Pharmacy Health and Wellness.<sup>728</sup> The memo made it clear that Walgreens’ Bennett was an active participant in Purdue’s efforts to

<sup>723</sup> PPLPC014000362725, at -2738.

<sup>724</sup> PPLPC004000170400; PPLPC004000170402.

<sup>725</sup> PPLPC004000317516 (produced natively), at \*7.

<sup>726</sup> PPLPC004000377572.

<sup>727</sup> PPLPC014000362725 at -2738.

<sup>728</sup> PKY180267742 at -7742.

promote OxyContin, not a passive recipient of their promotional campaign. She offered her own original ideas to help support Purdue's efforts to sell more OxyContin. Further, she shied away from actions that might decrease sales, even when those actions appropriately highlighted the risks of opioids.

- A. During their discussion of educational efforts targeting pharmacists, "Sheila volunteered the fact that it is much wiser for us, and cost effective, to do, what she called, Regional Level Market Programs. She indicated that instead of getting 30 or 40 pharmacists at a time, a Market Program should get 250-300 and address a market as opposed to just one district."<sup>729</sup> In other words, Walgreens' executive Sheila Bennett was giving Purdue executive Stephen Seid inside information on how Walgreens trains its pharmacists, allowing Purdue to reach a larger target audience than it otherwise would have.
- B. When Purdue executive Stephen Seid recommended that Walgreens find a way to disseminate Purdue's "Abuse and Diversion Brochure," Walgreen's Bennett "expressed some concern that distributing this would scare people off of CII's [schedule II opioids]. She said, once again, that she would encourage, at the store level, that they stock and dispense OxyContin."<sup>730</sup> That Bennett was reluctant to disseminate the brochure for fear it would "scare people off" is consistent with under-representing the true risks of opioids in order to promote consumption. Bennett should have been worried that people weren't scared enough, especially as the opioid epidemic was unfolding around them.
- C. Seid and Bennett discussed the problem of diversion of OxyContin and specifically the suspended distribution of OxyContin 160mg,<sup>731</sup> the equivalent of 16 Percocet in a single pill, putting patients at high risk of addiction. Bennett was "concerned about the message it sent to the trade and the public."<sup>732</sup> Although the exact nature of her concern was not characterized, we can infer that she was concerned that suspending distribution of OxyContin 160mg would 'scare off' customers. She then offered her own suggestions about "tracking of OxyContin 160mg and make it less attractive for diversion, i.e. selling it in smaller quantities."<sup>733</sup> That Bennett,

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<sup>729</sup> *Id.* at -7743.

<sup>730</sup> *Id.* at -7742.

<sup>731</sup> *Id.* at -7743-7744.

<sup>732</sup> *Id.* at -7744.

<sup>733</sup> *Id.*



a Walgreens executive, was offering suggestions about how to reinstate OxyContin 160mg, speaks to the active and collaborative role Walgreens' took to help Purdue promote OxyContin.

- D. Harkening back to 'opioid super stores', Seid wrote, "Sheila, and Walgreens, are very strong in their resolve that the stores are expected to stock what they have in the warehouse. She indicated that this was policy approved by the Chairman of the Board. They are very strong on this philosophy. She also indicated that *we will work with you, as much as we can, so that patients get what they need.*"<sup>734</sup>
- E. The memo further reveals that Walgreens, based on its own data, which it shared with Purdue and is reproduced below, was able to see that as the dose of OxyContin tablets went up, so too did the number of pills dispensed:<sup>735</sup>

**Average Prescription Size and Number of Prescriptions Written**

<b>STRENGTH</b>	<b>NUMBER OF PRESCRIPTIONS</b>	<b>AVERAGE PRESCRIPTION SIZE</b>
OxyContin 10mg	17,046	60 Tablets
OxyContin 20mg	26,517	65 Tablets
OxyContin 40mg	17,556	71.9 Tablets
OxyContin 80mg	6,413	80.9 Tablets
OxyContin 160mg	510	79.8 Tablets

- F. This alone should have been cause for concern, since studies clearly show that the higher the dose and quantity of opioids, the greater the risk of addiction. Escalating doses of prescription opioids over time directly correlated with rising opioid deaths.
- G. Instead, Stephen Seid interpreted these data as follows: "It is interesting to note that as the strength escalates, so do the number of tablets. It is also interesting to note that based on appropriate titration these numbers are very reasonable. This

<sup>734</sup> *Id.* (emphasis in original)

<sup>735</sup> *Id.* at -7745.

underscores the fact that the vast majority of OxyContin scripts appear to be written and dispensed appropriately.”<sup>736</sup>

- H. In deposition testimony, Stephen Seid confirmed that Walgreens was one of the biggest dispensers of all of Purdue’s products including opioids,<sup>737</sup> and verified Purdue’s significant role in “educating” Walgreens pharmacists. He stated that Purdue “had a plethora of material as it related to distribution of products, anti-diversion strategies, and we would try to provide that material through [Walgreens corporate] at the state level,”<sup>738</sup> and that Purdue would not have been allowed to convey its messaging to Walgreens pharmacies without the permission (and approval) of Walgreens corporate.<sup>739</sup>
  - I. Furthermore, Seid testified to the communication between Purdue and Walgreens with regard to filling opioid prescriptions, recalling meetings with Walgreens executives where he would raise Purdue’s concerns about patients unable to get their opioid prescriptions filled at Walgreens.<sup>740</sup>
  - J. Stephen Seid was honored in 2015 by the distributor’s trade/lobbying association with the “Distribution Management Award for Industry Leadership”, citing his work at Purdue “educat[ing] retail pharmacy networks and distributors on minimizing drug diversion and opioid abuse.”<sup>741</sup>
- xxvi. Walgreens allowed Purdue sales reps to make calls on Walgreens Healthcare Supervisors who oversaw 70-100 retail stores.<sup>742</sup> In an internal email exchange dated June 18, 2015, Purdue’s Christopher Jarman described how Purdue DMs [District Managers] were allowed to go to Walgreens stores if given permission by Walgreens managers and “our sales reps can accompany.”<sup>743</sup>
- A. In reference to Walgreens, Purdue’s Christopher Jarman emphasized the importance of maintaining “a great business

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<sup>736</sup> *Id.*

<sup>737</sup> *Id.* at 45:10-19.

<sup>738</sup> *Id.* at 25:11-26:5. See also 48:22-52:9.

<sup>739</sup> *Id.* at 28:9-24. See also 67:20-72:19.

<sup>740</sup> *Id.* at 81:5-18.

<sup>741</sup> Healthcare Distribution Alliance, “HDMA recognizes former Purdue Pharma executive Stephen Seid with Distribution Management Award for Industry Leadership” (March 10, 2015) <https://www.hda.org/news/2015-03-10-hdma-recognizes-seid-with-dma-for-leadership>

<sup>742</sup> PPLPC014000362725, at -2740.

<sup>743</sup> PPLPC015000217960, at -7960.

relationship and with one of most important customers [sic].”<sup>744</sup>

- B. At a November 17, 2017 meeting between Purdue and Walgreens executives at “Walgreens University” at Walgreens’ corporate offices, it was noted that “Purdue was among the first to be selected and provided access to call on [Walgreens] Healthcare Supervisors” who each oversee between 70 and 100 retail stores.<sup>745</sup>

xxvii. Purdue was not Walgreens’ only collaborator.

- A. Endo sales representatives communicated directly to Walgreens pharmacists to increase dispensing of its products. A May 28, 2003 call to “Walgreens/141 Kearny” by Endo sales representative Jennifer DuPratt notes, “TT Christina, they carry the perc new levels and also the Lido patch,<sup>746</sup> *she says to talk to dr Broderick-at sutter he prescribes alot.*” (sic)<sup>747</sup>
- B. A June 2, 2003 call to “Walgreens/3601 California” by Endo sales representative Jennifer DuPratt notes “Spoke w/pharmacist, they carry the new levels of perc and the Lido patch. *Pharmacist helped me find Dr. Franklin Perry.*”<sup>748</sup> Endo’s sales call logs includes multiple calls from Endo sales reps (approx. 12 calls/visits) to Dr. Franklin Perry starting on June 3, 2003 through December 23, 2003. The notes state that Dr. Franklin “likes long lasting Oxycontin for chronic pain, likes perc for breakthrough. Loves lido.”<sup>749</sup> He said he has had some patients that have complaints and I combated each of them: not working, wont (sic) stay on, etc. We went over dosing info and he said he is going to offer Lido to every patient that comes in from now on. I will keep him stocked with samples, told him to remind his patients to wear it for 7 days to get full pain relief, Hope to get him to come to Lido dinner, will stop in next week with pharmacy update, dinner push and study. -Need to bring in Katz study.”<sup>750</sup>

<sup>744</sup> *Id.* at p. -7961.

<sup>745</sup> PPLPC014000362725, at -2740.

<sup>746</sup> “Lido” refers to a Lidocaine/non-opioid pain reliever patch sold by Endo.

<sup>747</sup> ENDO-OPIOID\_MDL-07391949 (emphasis added)

<sup>748</sup> ENDO-OPIOID\_MDL-07391949 (emphasis added)

<sup>749</sup> “Lido” refers to a Lidocaine/non-opioid pain reliever patch sold by Endo.

<sup>750</sup> ENDO-OPIOID\_MDL-07391949 (emphasis added)

- C. A July 14, 2003 call to “Walgreens/498 Castro” by Endo Sales representative Jennifer DuPratt notes “confirmed they have all products, *showed me book and most dr have converted to the new perc*<sup>751</sup> levels. Asked them to help remind dr.s”<sup>752</sup>
- h. Pharmacy Defendants allowed their pharmacists to be detailed by opioid manufacturers including Purdue and Endo.
- A. Endo’s Percocet sales call notes from 2003 show that sales representatives were detailing pharmacists, doctors, and even dentists.<sup>753</sup> Endo’s Percocet call notes from 2013 show that sales representatives were detailing Publix pharmacies in Marietta, GA<sup>754</sup> and a Kroger pharmacy in Kennesaw, GA.<sup>755</sup>
- B. A note for a May 15, 2003 Percocet call to Dr. Demagone in Ohio indicates that the doctor saw 80 patients per day and was willing to write Percocet for workers’ comp patients. The note also shows that the same sales representative who identified Dr. Demagone then communicated with CVS pharmacist Tracy who committed to ordering Percocet and also to reaching out to Dr. Demagone directly.<sup>756</sup>
- C. In a call note from May 27, 2003, an Endo sales representative reported telling a dentist whose patients were having a hard time filling 7.5mg Percocet prescriptions, that he “will double check with Walgreens on Lombard/Davis to make sure they stock, but in future call me and I can direct patients to facility.”<sup>757</sup>
- D. An August 21, 2003 call from Endo sales representative Marion Allyn to Clint Potter, MD, (noted specialty of “Pain Medicine”) notes, “O: *doc will write Lido and Perc*;®invited doc and Jim Buck to Oct Lido dinner; *discussed sending pts w/scripts to Walgreen’s*; doc states Lido is now part of standard therapy, as is Perc 325;”<sup>758</sup>

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<sup>751</sup> “Perc” refers to Percocet, a combination of the opioid oxycodone with acetaminophen.

<sup>752</sup> ENDO-OPIOID\_MDL-07391949. The Katz article, discussed in Appendix I.D, below, appears in Endo’s promotional strategy for Opana, is evidence that drug sales representatives used this dubious data point to promote opioids to doctors.

<sup>753</sup> ENDO-OPIOID\_MDL-07391949

<sup>754</sup> ENDO-OPIOID\_MDL-07391949 (See rows 6656, 9420, 68850, 75211, 78262, 145206)

<sup>755</sup> *Id.* (See row 243283)

<sup>756</sup> ENDO-OPIOID\_MDL-07391949

<sup>757</sup> *Id.*

<sup>758</sup> ENDO-OPIOID\_MDL-07391909 (emphasis added)

- E. Also, a February 5, 2004 call to Jules Steimnitz, MD from Endo sales representative Marion Allyn notes, “O: *doc will write Lido and Perc*;@discussed successes w/Lido; discussed Perc 2.5 and pt selection; doc expressed interest; *told him it is stocked in Walgreen up the block*; doc will attend UCSF ground rounds tonight.”<sup>759</sup>
- F. Notes from a January 2009 meeting between Johnson & Johnson and 6 CVS Pharmacy Supervisors included discussion about the launch of a new Tapentadol opioid product. “CVS request[ed] assistance in determining which stores should stock this product – which physicians are the highest volume pain management prescribers and where do their patients go?”<sup>760</sup> A key take-away from the meeting was CVS’s “willingness to work with us for stocking a scheduled medication and the local communication issues around stocking and inventory levels. Their mantra for 2009 is all about customer service and they want to ensure that they do not lose any scripts due to the narcotic form 222 required and the 3 day turn around for delivery.”<sup>761</sup>
- i. Pharmacy Defendants failed to adequately respond to “red flags” for misuse and diversion or support individual pharmacists in these efforts; and failed to use or analyze their own dispensing data to assist pharmacists in identifying prescriber-related red flags.
  - i. It is generally understood that the term “red flags” refers to a warning sign of danger. In the area of prescribing controlled substances, the term “red flags” has a similar meaning, and in particular a red flag is a warning sign that a particular prescription presents risk to the patient, a risk of diversion to unauthorized users, or both.
  - ii. In my own practice as an addiction medicine psychiatrist at Stanford for over 20 years, I have treated thousands of patients for addiction and dependence on prescription opioids, and the need for diligent investigation of red flags is an ever-present and recurring topic of discussion with the pharmacists who fill prescriptions for my patients, especially when controlled substances are prescribed.
  - iii. My relationship with pharmacists is collaborative, with the mutual goal of protecting the best interests of patients in receiving the proper medication, and the best interests of the community as a whole in preventing controlled substances from diversion to unauthorized users. Pharmacists regularly contact me to verify that I have prescribed the

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<sup>759</sup> ENDO-OPIOID\_MDL-07391912 (emphasis added)

<sup>760</sup> JAN-MS-00470438, at -0439.

<sup>761</sup> JAN-MS-00470438.

medication presented by the patient, or to inform me of any concerns they may have about the prescription. It is my practice to consult the PDMP, and it is my expectation that the pharmacist will also do so, to determine whether, for example, the patient has a pattern of early refills for controlled substances, has been on high doses or longer duration of controlled substances than medically indicated, has obtained multiple prescriptions from different prescribers for the same controlled drug or drug class (*e.g.*, opioids), has obtained multiple prescriptions for controlled substances from multiple different pharmacies, or has any contemporaneous or overlapping prescriptions that could increase the risk of adverse events (*e.g.*, an opioid and a benzodiazepine, which synergistically increase risk of respiratory depression and death).

- iv. In earlier years of the opioid epidemic, I frequently found evidence in the PDMP that patients had filled multiple opioid prescriptions, or filled opioid prescriptions when they had also received prescriptions for benzodiazepines, or re-filled opioid prescriptions early, which indicated to me that pharmacists had either not checked the PDMP before dispensing, or that they dispensed such prescriptions despite such red flags. Over the last several years, I have observed fewer such episodes, and I have also experienced an increase in the frequency with which pharmacists reach out to me to discuss controlled substance prescriptions for my patients.
- v. I have also regularly consulted PDMP/CURES, with regard to my own patients, and in such searches I have frequently discovered evidence of inadequate prior review by pharmacists or other physicians, resulting in illegitimate prescribing such as early refills, doctor shopping, and drug “cocktails” indicative of diversion.
- vi. I am familiar with the CSA and the regulations under the CSA assigning physicians the responsibility for proper prescribing for legitimate medical purposes and assigning a “corresponding responsibility” to pharmacists.<sup>762</sup> These provisions formalize the *collaborative relationship*, described above, that should exist between doctors and pharmacists, for the protection of patients and the community from the dangers of controlled substances. I am aware,

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<sup>762</sup> 21 C.F.R. §1306.04 provides, “(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.” 21 C.F.R. §1306.06 further provides, “Persons entitled to fill prescriptions. A prescription for a controlled substance may only be filled by a pharmacist, acting in the usual course of his professional practice and either registered individually or employed in a registered pharmacy, a registered central fill pharmacy, or registered institutional practitioner.”

through my review of Industry documents and DEA enforcement decisions, that the CSA and its regulations have been interpreted as applicable to both *pharmacies* and *pharmacists*.

- vii. An integral part of the pharmacists' corresponding responsibility entails the detection and investigation of red flags. These include perennial indicators that pertain across time periods, such as patients traveling unusual distances to get a prescription filled at a particular pharmacy; paying cash rather than using insurance; irregularities on the face of a prescription that may indicate forged or altered prescriptions; or patients' behaviors that create suspicion of drug misuse and addiction. Other red flags may evolve over time, such as those relating to medical knowledge of the risks of co-prescribed medications, development of dose and duration limits, and new or changing patterns of drug use among those misusing or addicted to prescription drugs, *e.g.*, drug "cocktails."<sup>763</sup>
- viii. In a 2014 video called "Red Flags," the National Association of Boards of Pharmacy (NABP) stated that "by recognizing red flags to help establish the validity of a prescription, the pharmacist becomes the last line of defense in preventing misuse."<sup>764</sup> I agree with this statement. The presence of a red flag does not require automatic refusal to dispense, and there may be some such warning signs that can be resolved. However, pharmacies are required to implement effective controls and procedures to guard against theft and diversion,<sup>765</sup> and red flags cannot be detected or resolved if such controls or procedures do not exist, if they are not monitored, or if they are undermined or contradicted by actual practices.
- ix. Similarly, the former Deputy Assistant Administrator for DEA's Office of Diversion Control has stated, "When registrants at every level—practitioners, pharmacies and distributors—fail to fulfill their obligations," the CSA's "necessary checks and balances collapse... Because pharmacies are the entity providing the controlled substances to the end user, they are often the last major line of defense in the movement of legal pharmaceutical controlled substances from legitimate channels into the illicit market. It is, therefore, incumbent on pharmacies to ensure that controlled substances are only dispensed pursuant to valid

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<sup>763</sup> See, *e.g.*, discussion of opioid-benzodiazepine cocktails at subsections *e* and *f*, below.

<sup>764</sup> Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020) <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 24, paragraph 86.

<sup>765</sup> See, Deposition of Demetra Ashley, In re: National Prescription Opiate Litigation (MDL No. 2804, Case No. 17-md-2804), March 11, 2021, at 104:15-107:19.



prescriptions issued for legitimate medical purposes in the usual course of professional practice.”<sup>766</sup>

- x. It is clear that “Performance Metrics” based on fill quotas and wait times significantly influence pharmacy conduct and care. According to a survey by the NABP, 83% of surveyed pharmacists believed that distractions due to performance metrics or measured wait times contributed to dispensing errors and that 49% felt specific time measurements were a significant contributing factor, which could reduce time for Drug Utilization Reviews (DURs) and ultimately result in unsafe conditions.<sup>767</sup> These concerns are particularly acute with respect to controlled substances and the need to diligently investigate red flags through PDMPs, DURs, and other means. Pharmacy policies and procedures may purport to impose requirements of sound professional judgment, while establishing impressive lists of red flags and investigative methods, but these offer little protection when pharmacists are overwhelmed by the need to meet such performance metrics.
- xi. An article in a pharmacy professional journal stated: “Chain stores often require pharmacists to dispense 300 or more prescriptions a day, which translates to 37.5 prescriptions an hour in an 8-hour shift; that in turn translates to 1.6 minutes per prescription, during which time a pharmacist must verify the accuracy of the label, check the patient profile for duplications/interactions, contact prescribers if any issues arise, call the insurer as needed, verify that the contents of the prescription vial are accurate, and counsel the patient on the medication - impossible!”<sup>768</sup> Similarly, A University of Arizona College of Pharmacy study found that pharmacists’ workload threatened public safety, and that prescribing errors such as drug-drug interactions increased by 3% for every additional prescription filled per hour.<sup>769</sup> ¶
- xii. An investigation of prescribing practices conducted by the Chicago Tribune in 2016 found that 49% of chain pharmacies committed fundamental errors in dispensing prescriptions of two medications that were contraindicated for concurrent use, due to risks of severe and

<sup>766</sup> MNK-T1\_0008415650 at -5653. Declaration of Joseph Rannazzisi, submitted in *Holiday CVS, L.L.C., v. Holder*, Civ. No. 1:12-cv-191 (D.D.C Fed. 24, 2012).

<sup>767</sup> National Association of Boards of Pharmacy. Performance Metrics and Quotas in the Practice of Pharmacy (Resolution 109-7-13), (June 5, 2013). <https://nabp.pharmacy/news/news-releases/performance-metrics-and-quotas-in-the-practice-of-pharmacy-resolution-109-7-13/>

<sup>768</sup> Anna Leon Guerrero, *Pharmacy staffing levels can threaten patient lives*, Drug Topics (Nov. 4, 2015), [https://www.drugtopics.com/view/pharmacy-staffing-levels-can-threaten-patient-lives\\_](https://www.drugtopics.com/view/pharmacy-staffing-levels-can-threaten-patient-lives_)

<sup>769</sup> Daniel C. Malone, *Pharmacists’ Workload Contributes To Errors*, Science Daily (Apr. 24, 2007), <https://www.sciencedaily.com/releases/2007/04/070424130317.htm>.

potentially fatal adverse effects, without warning customers of the dangers. The investigators tested 255 pharmacies and found, “CVS, the nation’s largest pharmacy retailer by store count, had the highest failure rate of any chain in the Tribune tests, dispensing the medications with no warning 63 percent of the time. Walgreens, one of CVS’ main competitors, had the lowest failure rate at 30 percent — but that’s still missing nearly 1 in 3 interactions.”<sup>770</sup> Walmart pharmacies committed similar errors at a rate of 43 percent. While some pharmacists did properly warn, “in test after test, other pharmacists dispensed dangerous drug pairs at a fast-food pace, with little attention paid to customers. They failed to catch combinations that could trigger a stroke, result in kidney failure, deprive the body of oxygen or lead to unexpected pregnancy with a risk of birth defects.”<sup>771</sup> The Tribune reporters said that their 2-year study “exposes fundamental flaws in the pharmacy industry. Safety laws are not being followed, computer alert systems designed to flag drug interactions either don’t work or are ignored, and some pharmacies emphasize fast service over patient safety. Several chain pharmacists, in interviews, described assembly-line conditions in which staff hurried to fill hundreds of prescriptions a day.”

- xiii. These failures to follow safety laws, and the emphasis on fast service over patient safety, are all the more important with controlled substances such as prescription opioids, due to their inherently addictive and potentially fatal consequences. Dispensing the combination of opioids and benzodiazepines, as Defendant Pharmacies did, carried particularly grave risks, and the sources referenced above support my opinion that such prescriptions were frequently issued without warnings of increased dangers.
- xiv. Significantly, the sources cited above were not exclusive to controlled substances, where the need for time to conduct diligent review is crucial to public health. Staggering numbers of prescription fills required by quotas and performance metrics are antithetical to the “sound professional judgment” that pharmacists must attempt to exercise under such conditions, making a mockery of the policies and procedures that impose such impossible standards.
- xv. I have reviewed the policies and procedures of Defendants in this case, as well as documents from the National Association of Chain Drug Stores (NACDS), medical literature relating to risks of prescription opioids and benzodiazepines (such as alprazolam, or Xanax) and muscle relaxants (such as carisoprodol, or Soma), and DEA decisions referencing those risks in the context of enforcing the CSA against

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<sup>770</sup> Sam Roe et al., *Pharmacies Miss Half of Dangerous Drug Combinations*, Chi. Tribune (Dec. 15, 2016), <https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html>.

<sup>771</sup> *Id.*

pharmacies, and I have evaluated that information in light of my experience and expertise.

- xvi. Based on this evaluation, it is my opinion that Pharmacy Defendants lacked policies and procedures to adequately investigate and resolve red flags of diversion and risk of medical complications during the first decade or more of the opioid epidemic; that even after certain policies and procedures were adopted, they were inadequate to meet the obligation to detect and resolve red flags before dispensing; that Pharmacy Defendants could and should have analyzed its own data to assist pharmacists in identifying prescriber-related red flags<sup>772</sup>; and that Pharmacy Defendants implemented counter-productive measures, such as time pressures to fill prescriptions, financial incentives for rapid prescription fills, understaffing, permissive rather than mandatory use of PDMP resources, and failure to use their own data resources, which impaired pharmacists' ability to carry out their responsibilities to investigate red flags. As further detailed below, Pharmacy Defendants also failed to adequately respond to complaints from pharmacists who were concerned about pill mill prescribers and other abuses.
- j. Risk of opioids and benzodiazepines in combination: Because of the particular importance of the red flag for co-prescribing of opioids and benzodiazepines, particular attention to the evidence of increased risk is provided below. In short, the risk is two-fold. First, it has been known since at least 2002 that the addition of a benzodiazepine in a patient taking opioids increases the risk of respiratory depression, and this has accurately been described by an AMA speaker as a "potentially deadly combination."<sup>773</sup> Second, it has been known since at least 2005 that prescription opioid patients seek benzodiazepines to accentuate the "high" of the opioid drug, thereby increasing the likelihood that either will be diverted for improper use.<sup>774</sup>
- i. Based on Pharmacy Defendants' own documents, it is my opinion that they had an obligation to be aware of both the evolving medical literature and DEA enforcement actions, in determining the proper identification and resolution of red flags. In my opinion, as explained below, Pharmacy Defendants failed to adequately identify or resolve a host of red flags, and, in particular, the dangerous co-prescribing of opioids and benzodiazepines.

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<sup>772</sup> These include overprescribing, prescribing of higher dosages, prescribing patterns, and proportions of controlled substance/non-controlled prescribing.

<sup>773</sup> "Dr. Patrice Harris Talks About Opioids" The Augusta Chronicle, August 12, 2018  
<https://www.youtube.com/watch?v=kbToYDmh16M>

<sup>774</sup> *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, 66,163 (Oct. 27, 2010).

- ii. Medical literature has shown the increased risk of fatal respiratory depression by adding benzodiazepines to opioids since 2002.
- iii. In 2002, a peer-reviewed article analyzed mortality among patients taking the opioid methadone, and concluded: “Benzodiazepines are more likely to contribute to fatal methadone toxicity in newly admitted maintenance patients and those taking methadone tablets for pain relief.”<sup>775</sup>
- iv. In, 2007, a peer-reviewed article stated: “As central nervous system (CNS) depressants, benzodiazepines have been shown to act synergistically with opioids to reduce respiratory function, thereby increasing the risk of fatal and non-fatal overdose with opioids such as methadone and heroin.”<sup>776</sup>
- v. In 2012, a peer-reviewed investigation stated: “The co-abuse of BZDs and opioids is substantial and has negative consequences for general health, overdose lethality, and treatment outcome. Physicians should address this important and underappreciated problem with more cautious prescribing practices, and increased vigilance for abusive patterns of use. ...Although BZDs are a widely used practice for treatment of anxiety disorders, efforts must be taken to prevent the potentially lethal interaction that can occur when opioids and BZDs are administered simultaneously.”<sup>777</sup>
- vi. In 2013, a Research Letter prepared by CDC officials stated, based on 2010 mortality data, “Opioids were frequently implicated in overdose deaths involving other pharmaceuticals. They were involved in the majority of deaths involving benzodiazepines (77.2%), antiepileptic and antiparkinsonism drugs (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%). Among overdose deaths due to psychotherapeutic and central nervous system pharmaceuticals, the proportion involving only a single class of such drugs was highest for opioids (4903/16 651; 29.4%) and lowest for benzodiazepines (239/6497; 3.7%).”<sup>778</sup> This means that benzodiazepines alone are infrequently fatal, but frequently contribute to prescription opioid deaths.

<sup>775</sup> Caplehorn, J. R., *et al.* Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health*, 26(4), 358–363 (2002). <https://doi.org/10.1111/j.1467-842x.2002.tb00185.x>. (emphasis added).

<sup>776</sup> Nielsen, S., *et al.* Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. *Addiction* (Abingdon, England), 102(4), 616–622. (2007) <https://doi.org/10.1111/j.1360-0443.2006.01731.x>. (emphasis added).

<sup>777</sup> Jones, J. D., *et al.* Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug and Alcohol Depend.*, 125(1-2), 8–18. (2012) <https://doi.org/10.1016/j.drugalcdep.2012.07.004>., (emphasis added).

<sup>778</sup> Jones, *et al.*, Pharmaceutical Overdose Deaths, United States, *JAMA* 2013;309(7):657-659. 2010. doi:10.1001/jama.2013.272

- vii. These sources show that the danger of co-prescribing opioids and benzodiazepines was known in the medical literature by 2002 and reaffirmed thereafter. A recent summary publication by the National Institute on Drug Abuse stated: “Every day, more than 136 Americans die after overdosing on opioids. However, *between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67%, from 8.1 million to 13.5 million.* The quantity obtained also increased from 1.1 kg to 3.6 kg lorazepam-equivalents per 100,000 adults. Combining opioids and benzodiazepines can be unsafe because both types of drug sedate users and suppress breathing—the cause of overdose fatality—in addition to impairing cognitive functions. Unfortunately, many people are prescribed both drugs simultaneously. In a study of over 300,000 continuously insured patients receiving opioid prescriptions *between 2001 and 2013, the percentage of persons also prescribed benzodiazepines rose to 17 percent in 2013 from nine percent in 2001.* The study showed that people concurrently using both drugs are at higher risk of visiting the emergency department or being admitted to a hospital for a drug-related emergency. Previous studies have also highlighted the dangers of co-prescribing opioids and benzodiazepines. A cohort study in North Carolina found *that the overdose death rate among patients receiving both types of medications was 10 times higher than among those only receiving opioids.* In a study of overdose deaths in people prescribed opioids for noncancer pain in Canada, 60 percent also tested positive for benzodiazepines. A study among U.S. veterans with an opioid prescription found *that receiving a benzodiazepine prescription was associated with increased risk of drug overdose death in a dose-response fashion.*”<sup>779</sup>
- viii. In 2018, I co-authored an article, entitled, “Our Other Prescription Drug Problem,” which discussed the dangers of prescribing benzodiazepines contemporaneously with opioids.<sup>780</sup> In this article, we noted that FDA had imposed a heightened warning of the dangers of co-prescribing these drugs, and we also referenced the importance of checking the PDMP to prevent such inappropriate use. The same recommendation is equally applicable to Walgreens and its pharmacy practices, and for the same reason: to prevent diversion and reduce risk of addiction, overdose and death.
- ix. Co-prescribing of opioids and benzodiazepines has been a target of DEA enforcement of the CSA since at least 2005.
- x. As noted above, the co-prescription of benzodiazepines and opioids presents a significant risk of diversion due to the increased “high”

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<sup>779</sup> National Institute on Drug Abuse. Benzodiazepines and Opioids, (Feb. 3, 2021).

<https://www.drugabuse.gov/drug-topics/opioids/benzodiazepines-opioids>. (emphasis added)

<sup>780</sup> *N Engl J Med.* 2018;378(8):693-695, fn. 12, above.

compared to opioids alone, and this combination has been the subject of numerous DEA enforcement actions, including those summarized below. The Pharmacy Defendants' own documents show their awareness of the need to be cognizant of DEA enforcement actions in devising effective controls against diversion.

- xi. In the *East Main Street Pharmacy* case, revocation of a pharmacy's DEA Certificate of Registration was affirmed where the pharmacy filled large quantity of prescriptions "for a benzodiazepine, two narcotic pain medications, and Soma, and '[t]hese drug combinations are generally known in the medical and pharmacy profession as being favored by drug-seeking individuals.'" <sup>781</sup> The prescriptions at issue were dispensed between September 2005 and February 2006. <sup>782</sup> This decision also addresses the relationship between prescribing of "cocktails" and other red flags, as follows: "Respondent repeatedly dispensed drug cocktails for multiple controlled substances including oxycodone, hydrocodone, and alprazolam, as well as carisoprodol, a combination which is widely known in the pharmacy profession as being popular with drug abusers, and it did so in such quantities that any reasonable pharmacist would have asked how the prescriptions could possibly serve a legitimate medical purpose. The Government's Expert also explained that these cocktails would have a synergistic effect on a person's central nervous system and could cause respiratory depression. Accordingly, even if Volkman [the prescribing MD] told Mr. Fletcher [the pharmacist] that he did blood tests and MRIs, this would not make the prescriptions any more legitimate. *This alone supports the conclusion that Mr. Fletcher violated Federal law in dispensing the Volkman prescriptions.* 21 CFR 1306.04(a). The other evidence—such as that related to the quantities of the various drugs being prescribed, the dosing, and lack of individualization of therapy; the distances the patients were travelling and the typical method of payment; the fact that Mr. Fletcher knew that other pharmacists had refused to fill Volkman's prescriptions; the percentage and number of Volkman's prescriptions that were for controlled substances—is simply icing on the cake." <sup>783</sup> Thus, the red flag of cocktail prescribing was sufficient to impose the duty of investigation before dispensing, regardless of the other listed red flags.
- xii. The *Holiday CVS* case involved a number of different red flags at a CVS pharmacy in Florida, where DEA agents had gone to pharmacies across the State to discuss drug diversion problems. The decision in the

<sup>781</sup> East Main Street Pharmacy; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, (Oct. 27, 2010), at 66,149.

<sup>782</sup> *Id.* at 66,159.

<sup>783</sup> *Id.* at pp. 66164-65. (emphasis added)



case included a statement that, “As an example of a red flag of diversion which would have been discussed during these DEA outreach programs, DI [DEA Investigator] Langston identified “a lot of prescriptions coming in for oxycodone, 30 milligrams (mg), oxycodone, 15 [mg]; Xanax [alprazolam] two [mg].”<sup>784</sup> “Indeed, in a December 2010 meeting, DEA Investigators explained to CVS officials various red flags to look for including the prescribing of the combination of oxycodone and alprazolam.”<sup>785</sup> In the same case, the DEA’s expert testified, “Well, from a clinical pharmacist perspective that combination of drugs is what I would call a red flag because alprazolam and oxycodone are commonly diverted to nonmedical use.”<sup>786</sup>

- xiii. In the *Pharmacy Doctors Enterprises d/b/a Zion Clinic Pharmacy* DEA action, one of the red flag subjects of enforcement was described as follows: “The Show Cause Order alleged that Respondent filled opiate (hydromorphone) and benzodiazepine (alprazolam, clonazepam, diazepam, or lorazepam) prescriptions, a ‘common “drug cocktail” popular with drug abusers,’ for the same customer on the same day at about the same time without first having resolved the red flags of diversion. The Show Cause Order cited 14 prescriptions, or seven pairs of ‘drug cocktail’ prescriptions, that Respondent allegedly filled during the period of October 2012 through January 2013.”<sup>787</sup> The court stated, regarding the DEA’s expert: “Dr. Gordon addressed whether a muscle relaxant had to be present to constitute a drug cocktail. She stated that, ‘Cocktail medications usually . . . are a combination of an opioid plus or minus a benzo plus or minus a muscle relaxant’ ... Then she explained: ‘But what I’ve seen . . . lately is the doctors have stopped the Soma, and they are just doing, now, high doses of Dilaudid, high doses of benzos. It used to be Oxys. Now they’ve switched to hydromorphone. So you see . . . the flags change.’ She added that, ‘I see the physicians and drug diverters trying to eliminate one of the components of the cocktail to try to get away with diverted drugs.’”<sup>788</sup> The Court concluded: “Based on all of the evidence in the record, I find that Respondent filled prescriptions without having resolved the red flags of customers presenting prescriptions with a combination of an

<sup>784</sup> *Holiday CVS, L.L.C., d/b/a CVS/Pharmacy*, Nos. 219 and 5195; Decision and Order, 77 Fed. Reg. 62,316. (Oct. 12, 2012), at 62,325; <https://www.govinfo.gov/content/pkg/FR-2012-10-12/pdf/2012-25047.pdf>. . (emphasis added)

<sup>785</sup> *Id.* at 62,334.

<sup>786</sup> *Id.* at 62,333.

<sup>787</sup> *Pharmacy Doctors Enterprises d/b/a Zion Clinic Pharmacy*; Decision and Order, 83 Fed. Reg. 10,876 (Mar. 13, 2018), at 10,877 <https://www.federalregister.gov/documents/2018/03/13/2018-05020/pharmacy-doctors-enterprises-dba-zion-clinic-pharmacy-decision-and-order>, (emphasis added).

<sup>788</sup> *Id.* at p. 10,888.



opiate and a benzodiazepine which is a common ‘drug cocktail’ popular with drug abusers.”<sup>789</sup>

- xiv. The *East Main Street* case, which involved combinations that also included a muscle relaxant, would support a red flag for that combination as of the 2005-06 prescriptions that were the target of DEA enforcement.
- xv. In fact, pharmacists have known about the dangers and abuse potential of ‘drug cocktail’ prescribing long before 2005. According to the deposition testimony of Karen Mankowski, a pharmacist and former VP of Pharmacy Operations for both Rite-Aid and Meijer, co-prescribing of a narcotic, muscle relaxant and benzodiazepine, also called “the trinity or the atomic cocktail” was a known red flag since Ms. Mankowski “started filling prescriptions in 1978.”<sup>790</sup>
- xvi. In light of the materials summarized above, it is my opinion that a red flag for the combination of opioids and benzodiazepines should have been in place by no later than 2007, based on the medical literature, and by no later than 2010, based on DEA enforcement actions. The *East Main Street* case, which involved combinations that also included a muscle relaxant, would support a red flag for that combination as of the 2005-06 prescriptions that were the target of DEA enforcement. In light of the known risks to health, and the attraction of drug seekers to this combination, Pharmacy Defendants should have been particularly vigilant to identify, investigate, and resolve such red flags before dispensing.
- xvii. By 2005, the prescription opioid epidemic was several years into its evolution, having begun in the mid-to-late 1990s. As recounted previously in this Report, the medical literature, CDC data, and articles in the lay press had made clear that prescription opioids were the cause of a significant spike in overdose and mortality.<sup>791</sup> The DEA had already begun enforcement actions against pharmacies for failure to investigate or resolve red flags of diversion and increased risk of drug cocktails in 2005.<sup>792</sup> The need for effective controls against diversion had existed since the passage of the CSA, decades earlier, but that need was magnified by the prescription opioid epidemic in the early 2000s.

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<sup>789</sup> *Id.* at p. 10,889-90.

<sup>790</sup> Deposition Transcript of Karen Mankowski (July 7, 2022), In Re: National Prescription Opiate Litigation, Case Track 7 (Case No. 1:17-MD-2804) at 220:13-222:2.

<sup>791</sup> See Section §C.3 of this Report.

<sup>792</sup> *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149, (Oct. 27, 2010). (Which described misconduct in 2005-2006 as the basis for DEA enforcement.)

- xviii. Information about the severity of the epidemic and the risks of opioids continued to become widely known. On May 10, 2007, the New York Times reported that Purdue and three current and former executives “pleaded guilty today in federal court here to criminal charges that they misled regulators, doctors and patients about the drug’s risk of addiction and its potential to be abused.”<sup>793</sup> This widely publicized event gave further notice to Defendant Pharmacies, and to the world at large, that OxyContin, a very popular and profitable drug, carried major risks of abuse, and that the risks had been downplayed.
- xix. On January 10, 2013, the NACDS convened a meeting of the “DEA Compliance Working Group,” which included a Walgreens representative as Co-Chair, and representatives of CVS, Rite-Aid, Walmart and Meijer as “Participants.”<sup>794</sup> In advance of the meeting, NACDS circulated a legal overview of considerations for development and implementation of a voluntary, “industry-wide code for controlled substance dispensing;” an overview of DEA standards and red flags from recent DEA cases; and a summary of medical literature relevant to red flags for prescription drug abuse.<sup>795</sup> Significantly, NACDS cited “the need to be forward-thinking with the code, and go beyond simply codifying known ‘red flags’ for abuse.”<sup>796</sup> This statement, in a document that included input from all of the major chain pharmacies, shows that by 2013 an adequate system was not in place to prevent against misuse and diversion, and a better top-down system was needed across all stores.
- xx. A summary of the January 10, 2013 meeting, circulated to participants, stated that “Key elements” to be included in the code would be, “ensuring an appropriate prescriber-patient relationship, ensuring physicians have a relevant scope of practice for the prescribed medication, and focus of commonly abused cocktails.”<sup>797</sup>
- xxi. The January 2013 NACDS summary provided a table of red flags, broken into the categories of Patient Conduct, Physician Conduct, and Pharmacy/pharmacist Conduct.<sup>798</sup>
  - A. The “Patient Conduct” category included traveling significant distance to fill a prescription, paying in cash, behaviors

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<sup>793</sup> Meier, B., *In Guilty Plea, Oxycontin Maker to Pay \$600 Million*. New York Times (May 10, 2007). <https://www.nytimes.com/2007/05/10/business/11drug-web.html>.

<sup>794</sup> WAGMDL00496404; WAGMDL00496402

<sup>795</sup> WAGMDL00496404. *See also* WMT\_MDL\_000524163; WMT\_MDL\_000524168; WMT\_MDL\_000524176.

<sup>796</sup> WAGMDL00496404.

<sup>797</sup> *Id.* at 6405.

<sup>798</sup> WAGMDL00496407. *See also* WAGMDL00303281.

consistent with being under the influence of controlled substances, and “doctor shopping.” As to the latter, the NACDS proposed recommendations included, “Require the review of PDMP prior to dispensing all high-risk medication.”<sup>799</sup>

B. The “Physician Conduct” category included large numbers or percentages of controlled substance prescriptions; prescribing “high-alert drugs,” including opioids, benzodiazepines and barbiturates; and prescribing “questionable ‘cocktails’ of highly diverted drugs,” mentioning as examples, (a) oxycontin, an opioid + alprazolam, a benzodiazepine, and (b) the trinity of an opioid, a benzodiazepine, and a muscle relaxant. As to the “cocktails” red flag, the NACDS summary cited the *Holiday* and *East Main* DEA decisions, and the “Potential Action” included, “Leverage drug screening software to help identify cocktails through unique alert.”<sup>800</sup>

C. The “Pharmacy/pharmacist Conduct category included “Excessive volume and rate of growth of controlled substances,” and the NACDS Potential Actions included a mandatory 48-72 hour period for enhanced scrutiny of prescriptions for high-risk substances; removing controlled substances from dispensing incentive programs; or ceasing to carry high-risk products for dispensing.”<sup>801</sup>

xxii. On August 31, 2016, the FDA determined that the risk of benzodiazepines in combination with opioids was sufficient to warrant addition of a Boxed Warning, in response to a Citizen’s Petition requesting such action. The Petition itself was based on medical literature from prior years.<sup>802</sup> The FDA’s response to the Petition cited literature published between 1999 and 2014 in support of the statement

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<sup>799</sup> *Id.* at -6409.

<sup>800</sup> *Id.* at -6410-6415.

<sup>801</sup> *Id.* at -6415.

<sup>802</sup> See U.S. Food & Drug Administration, *New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines*, (August 31, 2016). Available at <https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-opioid-analgesics-prescription-opioid-cough-products-and> : “After an extensive review of the latest scientific evidence, the U.S. Food and Drug Administration announced today that it is requiring class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines. Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications at the same time. Risks include extreme sleepiness, respiratory depression, coma and death.”

that “in certain circumstances, either opioids or benzodiazepines independently can depress respiration. When combined, these drugs can cause greater respiratory depression than either drug would by itself, as can other CNS depressant drugs when combined with opioids. For this reason, the labeling of many opioid analgesics and benzodiazepine drugs currently contains warnings about the risks of concomitant use of opioid analgesics and benzodiazepines. To date, however, these warnings have not been presented in a boxed warning.”<sup>803</sup> The FDA’s action was explicitly based on past literature that documented the risk of this combination.

- xxiii. A 2018 review of PDMPs stated, “[M]andating that all prescribers and pharmacists enroll in PDMPs and requiring more frequent data reports would create a more unified fight against drug diversion. ... Because pharmacists verify countless controlled substances every day, they can greatly affect drug diversion. Reviewing the PDMP prior to dispensing could become a part of regular workflow, regardless if a pharmacist’s respected state mandates PDMP query and reporting. PDMPs may not be the sole solution to the opioid crisis or other drug diversion, but they represent progress in combatting the epidemic.”<sup>804</sup> I agree with these views. In particular, pharmacies could have, and should have, required PDMP review before dispensing prescription opioids and opioid combinations, without waiting for States to do so. At minimum, they should have analyzed their own databases to enable their pharmacists to limit diversion, by identifying prescriber-related red flags that would not have appeared in a profile of a particular patient.
- xxiv. For example, as reported in a 2015 “Overview of Purdue Programs” presentation, Purdue was able to track 2011-2012 national rates of doctor-shopping IR oxycodone [OxyContin] through IMS data showing overlapping prescriptions in combination with 2 or more prescribers and 3 or more pharmacies.<sup>805</sup> Review of state PDMPs by pharmacists and prescribers may well have reduced these numbers.

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<sup>803</sup> See Letter from Janet Woodcock to Leana Wen M.D. and Nicole Alexander-Scott M.D., RE: Docket No. FDA-2016-P-0689, U.S. Food & Drug Administration, Center for Drug Evaluation and Research, Available at [https://downloads.regulations.gov/FDA-2016-P-0689-0003/attachment\\_1.pdf](https://downloads.regulations.gov/FDA-2016-P-0689-0003/attachment_1.pdf), at p. 4, citing Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract.* 2014;27(1):5-16; Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008; 00(6):747-58; Gueye PN, Borron SW, Risede P, *et al.* Buprenorphine and midazolam act in combination to depress respiration in rats. *Toxicol Sci* 2002;65:107-14; White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction* 1999;94(7):961-972.

<sup>804</sup> Bulloch, M., "The Evolution of the PDMP." Pharmacy Times (July 25, 2018). <https://www.pharmacytimes.com/view/the-evolution-of-the-pdmp>

<sup>805</sup> Dover Deposition Ex. 13, at \*24 (produced natively). In a recent article by Wang et al, the authors conducted a meta-analysis of observational studies showing that the most significant risk factors for opioid overdose, after a

- xxv. According to the CDC, “In 2011 and 2012 respectively, Ohio and Kentucky mandated *clinicians* to review prescription drug monitoring program (PDMP) data and implemented pain clinic regulation. In these states, MME per capita decreased in 85% and 62% of counties, respectively, from 2010 to 2015.”<sup>806</sup> It is reasonable to conclude that required PDMP review by *pharmacies* would further reduce illegitimate prescription opioid exposure.
- xxvi. In 2013, a pharmacist and a physician co-authored a “Perspective” in the New England Journal of Medicine, “Abusive Prescribing of Controlled Substances — A Pharmacy View.”<sup>807</sup> After noting the dramatic rise in both prescribing of opioids and opioid-related mortality, the authors acknowledged that, under the Controlled Substances Act, “Pharmacies have a role to play in the oversight of prescriptions for controlled substances, and opioid analgesics in particular.”<sup>808</sup> They further stated, “Programs providing greater transparency regarding controlled-substance prescribing, such as *mandatory use of e-prescribing for all controlled substances and a national, uniform program of prescription-drug monitoring*, would help pharmacists and clinicians target interventions more accurately to help patients who are abusing medications.”<sup>809</sup> In my opinion, any chain pharmacy could and should have required “mandatory” checking of a PDMP for any State in which such a program was in place.
- xxvii. The Stanford-*Lancet* Commission Report found that that opioid stewardship can be improved through the use of PDMPs to prevent risky drug combinations, doctor shopping and to detect so-called pill mills.<sup>810</sup> PDMPs’ value “is undermined if they are hard to use or if prescribers and pharmacists receive no training in how to use them, do not use them consistently, or do not enrol [sic] to use them at all.”<sup>811</sup>
- xxviii. In the absence of mandatory review of state PDMP databases, and considering the typical time constraints to which Pharmacy Defendants

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history of overdose, were multiple dispensers and/or prescribers. The data on patients with multiple dispensers and prescribers was available to Purdue and could have been acted upon to reduce high risk opioid consumption. *See*: Wang L, *et al.* Predictors of fatal and nonfatal overdose after prescription of opioids for chronic pain: A systematic review and meta-analysis of observational studies. *CMAJ*. 2023;195(41):E1399-E1411.

<sup>806</sup> Centers for Disease Control and Prevention. State Successes, (Page Last Reviewed: July 29, 2019). <https://www.cdc.gov/drugoverdose/policy/successes.html>

<sup>807</sup> Betses M, Brennan T. Abusive prescribing of controlled substances – A pharmacy view. *N Engl J Med*. 2013;369(11):989-991.

<sup>808</sup> *Id.* at p. 989.

<sup>809</sup> *Id.* at p. 991 (emphasis added).

<sup>810</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 23. *See also* Lembke A. Be sure to check the PDMP before prescribing controlled medications. *Psychiatric News* (June 17, 2016). *See also* Lembke A, Papac J, Humphreys K. Our other prescription drug problem. *N Engl J Med*. 2018;378(8):693-695. These articles, published in 2016 and 2018, respectively, were written and submitted for review before I was retained as an expert witness in opioid litigation.

<sup>811</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 23.

pharmacists have been subjected, it is highly likely that substantial numbers of prescriptions were misused and/or diverted and further contributed to the epidemic.

- k. Defendant Walgreens failed to effectively control against diversion and undermined efforts of pharmacists to prevent diversion.
  - i. Despite policies purporting to meet requirements of a “corresponding responsibility” to assure that only legitimate prescriptions are filled, Walgreens failed to implement or enforce those policies, resulting in repeat DEA enforcement actions against Walgreens for both distribution and pharmacy violations.
  - ii. Financial Incentive plans based on profits and prescription sales inevitably conflict with the need for careful, diligent and inherently time consuming investigation of red flags for dispensing of controlled substances, and the DEA ultimately cited such programs as contributors to the prescription opioid epidemic.<sup>812</sup> I agree that these programs contributed to the epidemic and hindered, rather than helped, in the requirement of effective controls against diversion.
  - iii. A brief summary of Walgreens’ policies and procedures is set forth below, along with an account of the DEA enforcement actions required to address conditions that undermined the policies, including profit-based performance metrics, understaffing, and incentives for prescribing more opioids.
  - iv. On August 1, 1998, Walgreens adopted a “Good Faith dispensing” policy, which stated that a pharmacist “*must* use the elements of Good Faith dispensing in conjunction with state and federal controlled substances when filling *all* prescriptions. The pharmacist must determine if a prescription for a controlled substance is dispensed for a legitimate medical purpose.”<sup>813</sup> The policy included a list of several “questionable circumstances,” which would later be called red flags, including numbers of prescriptions from the same doctor, numbers of prescriptions sought to be filled by the same patient; unusual doses; unusual geographic distances between patient, prescriber and pharmacy; and “consistent prescr[ibing] of habit-forming drugs.”<sup>814</sup> A pharmacist becoming aware of one or more of such circumstances was instructed by the policy to “Not dispense the drug,” and to notify the pharmacy supervisor.
  - v. On March 24, 2003, Walgreens revised the Good Faith Practices, setting forth the same elements of Good Faith dispensing, but no longer

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<sup>812</sup> WAGMDL00709398.

<sup>813</sup> WAGMDL00093367 (emphasis in original).

<sup>814</sup> *Id.*



instructing the pharmacist to “Not dispense the drug” if such circumstances were present. Instead, the revised policy instructed the pharmacist to contact the prescriber to confirm the prescription; the prescription could then be filled if the prescriber was reached and confirmed it, but was not to be dispensed if the prescriber could not be reached, or if the prescriber did not confirm the prescription.<sup>815</sup> This represented a loosening of the prior policy, in that the pharmacist could dispense a controlled substance prescription confirmed by the prescriber, regardless of whether the prescriber had issued the prescription for a legitimate medical purpose. This is not simply a theoretical concern, as DEA enforcement decisions have stated that there are “circumstances in which calling the prescriber will not resolve the red flags because the red flags indicate that the prescriber is collaborating with the patient to divert drugs.”<sup>816</sup>

- vi. Walgreens’ revision dated June 18, 2004 added that a “*corresponding responsibility* rests with the pharmacist to ensure that controlled substance prescriptions are issued for a legitimate medical purpose by an individual practitioner in the usual course of professional practice,”<sup>817</sup> using the language of federal regulation Section 1306.04. Revisions in February and November 2005, and in June 2006, included similar provisions, and similarly allowed the pharmacist to dispense a controlled substance if the prescriber could be contacted and confirmed the prescription, regardless of whether the prescription was actually for a legitimate medical purpose, and to not dispense if the prescriber could not be reached or did not confirm the prescription.<sup>818</sup> The 2006 version changed the heading to “Good Faith Practices/Fraudulent Prescriptions,” adding instructions regarding contacting law enforcement and preservation of prescriptions upon receipt of the prescriber’s confirming that the prescription was not legitimate.<sup>819</sup>
- vii. In August 2007, Walgreens adopted a policy to prevent diversion of controlled substances, directed at the risk of employees or others improperly stealing or removing drugs from the pharmacy. This provision did not alter the prior policies regarding diversion through the more common means of filling potentially illegitimate prescriptions.<sup>820</sup>

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<sup>815</sup> WAGMDL00335012.

<sup>816</sup> *Holiday CVS, L.L.C., d/b/a CVS/Pharmacy* Nos. 219 & 5195, Decision & Order, 77 Fed. Reg. 62,316, 62,318 (Oct. 12, 2012).

<sup>817</sup> WAGMDL00335018 (emphasis in original).

<sup>818</sup> WAGMDL00335018, at -5024 and -5010. *See also*, WAGFLAG00019484.

<sup>819</sup> WAGFLAG00019484. *See also* WAGMDL00335020.

<sup>820</sup> WAGFLDEA00000271.



- viii. Walgreens' dispensing conduct attracted attention from the DEA, beginning a lengthy history of CSA violations, penalties, and agreements intended to require the company to implement effective controls, and to put an end to what DEA described as "direct and significant contributors to the epidemic of prescription drug abuse and diversion."<sup>821</sup> I agree with the DEA's statement that Walgreens' failures directly and significantly contributed to the opioid epidemic. Walgreens' management entered into consent agreements with DEA regarding these violations, so there can be no doubt that corporate leadership was on notice of the absence of effective controls against diversion.<sup>822</sup>
- ix. On September 30, 2009, the DEA issued an Order to Show Cause (OTSC) against a Walgreens pharmacy in San Diego, CA. The OTSC alleged that since at least January 2007 the pharmacy had been filling prescriptions from unlicensed physicians, filling prescriptions issued for other than a legitimate purpose, and otherwise dispensing controlled substances, including hydrocodone, to individuals that Walgreens knew or should have known were diverting the controlled substance.<sup>823</sup>
- x. In 2010, in response to a DEA investigation into issues in a California Walgreens and more than a decade after the 1998 adoption of its "Good Faith Dispensing" policy for controlled substances, Walgreens acknowledged that "no such training exists" for Walgreens retail employees dispensing controlled substances.<sup>824</sup>
- xi. Despite DEA attention, Walgreens continued to focus on increasing oxycodone sales while failing to prevent diversion. In an August 2010 email regarding oxycodone sales, a marketing pharmacy director wrote that "The busiest store in Florida is Orlando filling almost 18 Oxycodone RXs per day. We also have stores doing about 1 a day. Are we turning away good customers?"<sup>825</sup> Although the later comment pertained to a Florida pharmacy, the attitude reflected the corporate mentality of increasing sales.
- xii. In April 2011, Walgreens entered into a three year Administrative Memorandum of Agreement with the Department of Justice and DEA, applicable to all Walgreens pharmacies.<sup>826</sup> The agreement required Walgreens to "maintain a compliance program to detect and prevent

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<sup>821</sup> WAGMDL00768976; WAGMDL00709398

<sup>822</sup> WAGMDL00757802. *See also* WAGMDL00578350

<sup>823</sup> WAGMDL00768976

<sup>824</sup> WAGFLDEA00001861

<sup>825</sup> WAGFLDEA00000812

<sup>826</sup> WAGMDL00757802. *See also* WAGMDL00578350

diversion of controlled substances” that would include “procedures to identify the common signs associated with the diversion of controlled substances including but not limited to, doctor-shopping and requests for early refills.”<sup>827</sup> Walgreens was also required to “notify the local DEA office within two business days of a refusal to fill a prescription for controlled substances where such refusal is based on the Walgreens pharmacist’s determination that the prescription was forged, altered, and/or issued for other than a legitimate medical purpose by a practitioner acting outside the usual course of professional practice.”<sup>828</sup>

- xiii. In May 2011, shortly after Walgreens entered the April 2011 Memorandum of Agreement with the DOJ and DEA, Walgreens issued a Code of Conduct and General Training, highlighting values of “[h]onesty and integrity,” and stating a commitment to be fully compliant with federal and state laws and regulations regarding controlled substances. The Code stated, “Walgreens WILL NOT TOLERATE an illegal, unprofessional or unethical act by any team member, INCLUDING, BUT NOT LIMITED TO, THE UNAUTHORIZED SALE, POSSESSION, USE, OR DIVERSION OF CONTROLLED SUBSTANCES.”<sup>829</sup> The Code informed employees that violations would be subject to discipline, including possible termination, as well as possible arrest and prosecution. In an apparent reference to the Memorandum of Agreement, the Code closed with the following: “*Affirmation: By clicking the button below, I acknowledge that as of this date, (1) I have completed one hour of General Training on the requirements imposed by Walgreens’ Corporate Integrity Agreement with HHS Office of the Inspector General and by the Walgreens Compliance Program and (2) I have received, read and understood and will abide by the Walgreens Pharmacy and Health Care Code of Conduct. I further acknowledge that I understand that my supervisor and members of the Compliance Office staff are available to answer any questions that I may have regarding the computer-based training I have received.*”<sup>830</sup>
- xiv. In October 2011, Walgreens began training for “Good Faith Dispensing” focused on “three pillars: identifying suspicious prescriptions and customers, validating the legitimacy of prescriptions, and reporting questionable prescriptions to law enforcement when

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<sup>827</sup> WAGMDL00757802 at -7803.

<sup>828</sup> *Id.* at -7803.

<sup>829</sup> WAGFLDEA00000127, at -0127-0128 (emphasis in original).

<sup>830</sup> *Id.* at 00130.

appropriate.”<sup>831</sup> The Good Faith Dispensing policy at this time contained no reference at all to available state PMDP resources.<sup>832</sup>

- xv. A June 2012 revision to the “Good Faith Dispensing” policy recommended that “If available in your state, use the PDMP to obtain additional information to help determine the validity and confirm the appropriateness of the prescription.”<sup>833</sup>
- xvi. In October 2012, Walgreens began to develop a supplemental “Good Faith Dispensing” (GFD) policy as to a “manageable list” of “top drugs” in order to “put teeth around GFD for high risk products,” including oxycodone.<sup>834</sup> Walgreens also put in place a Controlled Substance Order Monitoring System because the “previous system would continue to send additional product to the store without limit or review which made possible the runaway growth of dispensing of products like Oxycodone, that played a roll [sic] in the DEAs investigation of Walgreens.”<sup>835</sup>
- xvii. In January 2013, a Walgreens “DEA Update” presentation stated, “In June we re-launched our Good Faith Dispensing policy. However, we have learned more about DEA’s expectations around GFD and we felt the steps we were taking with GFD did not go far enough. The game has changed; we can no longer rely on the ‘I spoke to the prescriber and he said it was okay.’ This is especially true when the prescriber may be assisting the patient to inappropriately use controlled substances. We are going down a different path now and we have to make sure that we are prepared. So, we are piloting the TD GFD [Targeted Drug Good Faith Dispensing] in FL and NV.”<sup>836</sup>
- xviii. The Speaker’s notes on a related “DEA Update” presentation prepared for Walgreens market leadership in the same time period acknowledged that “Realistically, bottom line, yes sales are going to be impacted. However, some would say that we shouldn’t even be filling some of these prescriptions.”<sup>837</sup>
- xix. In fact, the TD GFD pilot in Florida and Nevada did result in reduced sales for oxycodone in Florida and Nevada.<sup>838</sup> In the 18 months

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<sup>831</sup> WAGMDL00659802, at -9808-9809.

<sup>832</sup> WAGMDL00254698 (June 2011 revision)

<sup>833</sup> WAGMDL00254700

<sup>834</sup> WAGMDL01109078

<sup>835</sup> WAGMDL00021425

<sup>836</sup> WAGMDL00707642

<sup>837</sup> WAGMDL01013472, at -3482.

<sup>838</sup> WAGMDL00289179 (produced natively), at slides 2 and 4.

following DEA Orders to Show Cause and the introduction of the TD GFD pilot, “Las Vegas and Orlando have both decreased over 30% in scripts.”<sup>839</sup>

- xx. After pilot programs of TD GFD, including in Florida and Nevada, the TD-GFD requirement was rolled out nationwide in April 2013. As part of this roll out, Walgreens distributed a National TD GFD Policy, a Checklist, an FAQ list, set of talking points, a TD GFD PowerPoint, as well as information about its National Prescriber TD-GFD efforts and a document on Clinical Pain Management.<sup>840</sup>
- xxi. Walgreens stated the TD GFD “policy was developed to help guide pharmacists through their corresponding responsibility in determining that the prescription was written for a legitimate medical purpose before dispensing in good faith” and was “created to assist and support pharmacists in their professional judgment to fill or refuse a target drug.”<sup>841</sup> Beginning in April 2013,<sup>842</sup> Pharmacists and Technicians were required to complete the TD-GFD checklist when dispensing prescriptions for certain “Target Drugs.”<sup>843</sup> However, the “Target Drugs” were limited to single ingredient oxycodone, hydromorphone, and methadone, and the form was only to be completed for those prescriptions.<sup>844</sup> For all “Target Drugs,” the hardcopy TD GFD checklist was required to be completed before filling the prescription and in states with a PDMP, all pharmacists were “required to know how to access” their state PDMP and instructed to “review, print and attach to the checklist.”<sup>845</sup> Walgreens acknowledged that “documentation is vital”<sup>846</sup> to “Good Faith Dispensing” and urged its employees to “document, document, document”<sup>847</sup> because “not documenting or poor documentation is as good as not doing.”<sup>848</sup> The TD GFD policy has been revised a number of times, through at least 2018.<sup>849</sup>
- xxii. In 2013, Walgreens added hydrocodone to the TD GFD checklist in limited districts but chose to wait seven years to contemplate adding it

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<sup>839</sup> WAGMDL00015230, at -5235.

<sup>840</sup> WAGNYAG00006361

<sup>841</sup> WAGMDL01132111 at WAGMDL01132112

<sup>842</sup> WAGMDL00316360; WAGMDL00744586

<sup>843</sup> WAGMDL00573579

<sup>844</sup> WAGMDL00001246; WAGMDL00001151. *See also*: WAGMDL00744592.

<sup>845</sup> WAGMDL00744596, at -4606-4610 and -4613

<sup>846</sup> WAGMDL00049236. *See also*: WAGMDL00987029, at -7032.

<sup>847</sup> WAGMDL00060489; WAGMDL00060490, at -0493-0494.

<sup>848</sup> WAGMDL00250893

<sup>849</sup> WAGMDL00005358; WAGMDL00005359 (attaching revised iterations); *See also*: WAGMDL00303474; WAGMDL00303475.

nationally.<sup>850</sup> It was not until 2019/2020 that Walgreens internally considered adding hydrocodone as a “Target Drug” on a national scale.<sup>851</sup> At the same time Walgreens was drafting TD GFD, the DEA and FDA were in the process of finalizing the rescheduling of hydrocodone from Schedule III to Schedule II, in recognition of its greater propensity for addiction and abuse.<sup>852</sup> Walgreens participated in a coordinated effort through the NACDS and the pharmacy community as a whole to oppose the rescheduling, citing undue burden on millions of Americans who need access to pain medications.<sup>853</sup> Walgreens omitted hydrocodone from the “Targeted Drugs”, even though it was the top ranked generic drug by retail pharmacy dollars.<sup>854</sup> With so many hydrocodone prescriptions and so little money per prescription due to its generic status, spending the time to properly vet each hydrocodone prescription would have impacted profitability for Walgreens and other NACDS members. Walgreens calculated that pharmacists spent approximately 5 minutes completing each checklist, equating to an average of 150 hours/store per year.<sup>855</sup>

- xxiii. Neither the 2011 MOA nor Walgreens’ new policies reduced the amount of opioids flowing out the doors. In fact, a Walgreens compliance audit found a “significant *increase* in the number of CII prescriptions we are filling,” and the company sought to “formulate a plan prior to any potential review by outside agencies.”<sup>856</sup> In 2011, Florida stores were ordering so many bottles of OxyContin that a Walgreens CII Function Manager questioned “how they can even house this many bottle[s]”<sup>857</sup> and discussed with the Replenishment Buyer in Pharmacy Purchasing that pharmacies were ordering an “unbelievable” amount of “1,000 bottles per week,” all of which were being dispensed.<sup>858</sup> On the advice of Walgreens’s CSA Compliance Officer, Dwayne Pinon, Walgreens struck two questions from the audit regarding “pain clinic patients” because as Pinon stated “If these are legitimate indicators of inappropriate prescriptions perhaps we should consider not documenting our own noncompliance.”<sup>859</sup>

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<sup>850</sup> WAGMDL00053720; WAGMDL00864374

<sup>851</sup> WAGMDL00053720

<sup>852</sup> CVS-MDLT1-000106705 at CVS-MDLT1-000106712, CAH\_MDL2804\_00011925

<sup>853</sup> JAN-MS-00837963, Rite\_Aid\_OMDL\_0019442, PPLP004308925

<sup>854</sup> CAH\_FEDWV\_00387846 (pg. 48)

<sup>855</sup> WAGMDL00573579

<sup>856</sup> WAGFLDEA00001890

<sup>857</sup> WAGFLDEA00000852

<sup>858</sup> WAGFLDEA00000891

<sup>859</sup> WAGFLDEA00001890

- xxiv. Walgreens' conduct as a distributor also resulted in DEA enforcement actions. On September 13, 2012 the DEA issued an Order to Show Cause (OTSC) and Immediate Suspension Order (ISO) to Walgreens' Jupiter Florida Distribution Center.<sup>860</sup> The ISO stated that Walgreen's distribution center "failed to maintain effective controls against the diversion of controlled substances into other than legitimate medical, scientific, and industrial channels, in violation of 21 U.S.C. §823(b)(1)(e)(1)."<sup>861</sup> A DEA press release explained, "An ISO is served pursuant to Section 303 and 304 of the Controlled Substances Act, Title 21 U.S.C. §823 and 824 when a DEA-registered business or ('registrant') constitutes an *imminent danger to the public safety and suspends a registrant's ability to handle or distribute a controlled substance such as oxycodone, hydrocodone and others pending a judicial proceeding.*"<sup>862</sup> The DEA had previously served an Administrative Inspection Warrant (AIW) on Walgreens Jupiter and its top six retail pharmacies in Florida. "These administrative actions were to determine if these Walgreens' maintained a system in place that detects and reports suspicious orders to the DEA to prevent the diversion of control substances as governed by federal laws and the Control Substance Act relating to the proper distribution of control substances,"<sup>863</sup> and the OTSC discussed issues at the six pharmacies served by the distribution center.<sup>864</sup>
- xxv. The DEA's enforcement action highlighted the impropriety of Walgreens' pharmacy compensation program based on bonuses for the number of prescriptions filled, combined with efforts by Walgreens Corporate headquarters to increase oxycodone sales, which "served as an incentive for pharmacists and pharmacy technicians to ignore the 'red flags' of diversion presented by these prescriptions, many of which, in the proper exercise of the pharmacist's corresponding responsibility under 21 CFR §1306.04(a), should have resulted in a refusal to fill."<sup>865</sup> The Order also described instances where Walgreens ignored ample "indications that its pharmacies were direct and significant contributors to the epidemic of prescription drug abuse and diversion" including a pharmacy continuing to dispense oxycodone to a customer who had refused to return extra units accidentally provided to him and whose girlfriend indicated was an addict who viewed the extra

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<sup>860</sup> WAGMDL00709398. *See also*: WAGMDL00387653

<sup>861</sup> Press Release, DEA Serves A Suspension Order On Walgreens Distribution Center In Jupiter, Florida, Drug Enforcement Administration (September 14, 2012), <https://www.dea.gov/press-releases/2012/09/14/dea-serves-suspension-order-walgreens-distribution-center-jupiter-florida>

<sup>862</sup> *Id.*, emphasis added.

<sup>863</sup> *Id.*

<sup>864</sup> WAGMDL00709398

<sup>865</sup> *Id.* at -9403.



oxycodone as a “pot of gold,” continuing to fill prescriptions for a customer who left evidence she had smoked oxycodone in the pharmacy restroom, and continuing to fill oxycodone prescriptions for a customer who ran after learning the pharmacy had called law enforcement on the suspicion that his prescription was a forgery.<sup>866</sup>

xxvi. Kristine Lucas was the function manager for Class II narcotics at Walgreens’ Jupiter, Florida distribution center from April 2006 to December 2013 where she processed orders for pharmacies in 15 states and Puerto Rico and reported to the distribution center general manager Rob Varno.<sup>867</sup> She testified that in 2010 Walgreens pharmacies gradually started to order large amounts of opioids, progressing from “30 bottles a week. And then, it went to 90 bottles a week, and then 300 bottles a week, and then 600 bottles a week, and it just kept progressing more and more and more,” getting to the point where they started ordering “unrealistic, astronomical” amounts.<sup>868</sup> Lucas did make calls to pharmacists who were making these huge orders and asked if they were filling suspicious prescriptions, and “a couple different pharmacists” told her doing due diligence/investigating suspicious prescriptions “was not their job. They have a script, they will fill it.”<sup>869</sup> She testified that high volume orders would be flagged in reports but an hourly employee would just call the pharmacy to verify the order was the correct amount (e.g. 500 bottles and not 50 bottles), and if they couldn’t get a hold of somebody they would just let the order go through.<sup>870</sup>

xxvii. Lucas testified that she repeatedly sent emails to managers and executives at Walgreens about the large opioid orders because she felt like the “situation was a ticking time bomb” because “the numbers we were shipping out...there was no way the stores could control it, house it inventory, I didn’t see how they could possibly control it on their side in the amount we were shipping to them.” Lucas testified that she was concerned Walgreens would have a legal problem with the orders.<sup>871</sup> In response to Lucas’s expressions of concern, Walgreens corporate leaders took no action to stop the large shipments.

xxviii. In 2012, the DEA shut down the distribution center and based on Lucas’ conversations with the DEA agents, they were focused on the

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<sup>866</sup> *Id.* at -9405-9406.

<sup>867</sup> Trial Testimony of Kristine Lucas, *State of Florida v. Walgreen Co.* (Case No. 2018-CA-001438). April 12, 2022, at 611:17-616:3

<sup>868</sup> *Id.* at 623:14-625:20.

<sup>869</sup> *Id.* at 630:25-632:10.

<sup>870</sup> *Id.* at 633:3-634:15

<sup>871</sup> *Id.* at 635:15-636:15



high volume of opioids and that they weren't secure.<sup>872</sup> The same day that the DEA shut down the distribution center, Lucas had a meeting with general manager Rob Varno to discuss her concerns about the shutdown.<sup>873</sup> Lucas testified that Varno told her, "Here's what we're going to say," which she understood to mean that a story was going to be "concocted," and "there was going to be some sort of justification for why we were shipping out the volume we were shipping out or not controlling the drugs just because of the vast amount that we were shipping out."<sup>874</sup> With respect to her emails complaining about the large shipments, Lucas testified as follows:

Q. Ms. Lucas, after the meeting with the lawyers, did you check on the status of your emails on the system?

A. Yes.

Q. What was the status?

A. They were gone.

Q. Were you able to access them anywhere on the email system or computer system?

A. No.

Q. And approximately how many emails had been on the system before they disappeared?

A. I'd say around 100.<sup>875</sup>

- xxix. Walgreens actions in Florida had nationwide consequences, helping to create a "Blue Highway" of oxycodone diverted from South Florida pill mills through the Appalachian and Ohio River Valley regions.<sup>876</sup>
- xxx. In November 2012, the DEA served Orders to Show Cause to three Walgreens pharmacies in Florida.<sup>877</sup> All three OTSCs reported similar circumstances of the pharmacies ignoring red flags for diversion.
- xxxi. On November 26, 2012, the DEA served on OTSC to a Walgreens pharmacy in Hudson, Florida, alleging that the pharmacy "ignored readily identifiable red flags that controlled substances prescribed were being diverted and dispensed controlled substances despite unresolved red flags."<sup>878</sup> The order noted that the pharmacy "dispensed controlled

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<sup>872</sup> *Id.* at 658:17-660:23

<sup>873</sup> *Id.* at 660:24-661:16

<sup>874</sup> *Id.* at 661:17-662:12

<sup>875</sup> *Id.* at 666:1-12.

<sup>876</sup> Higham, S., Horwitz, S. (2022). *American Cartel: Inside the Battle to Bring Down the Opioid Industry*. United States: Grand Central Publishing, Chapter 6.

<sup>877</sup> Press Release, *DEA Serves Order To Show Cause To Three Walgreens Pharmacies, Drug Enforcement Administration* (November 27, 2012), <https://www.dea.gov/press-releases/2012/11/27/dea-serves-order-show-cause-three-walgreens-pharmacies>

<sup>878</sup> WAGMDL00387708 at -7709-7713.

substances, primarily in suspicious cocktail combinations of oxycodone, alprazolam and carisoprodol, to patients of at least twenty (20) practitioners who were subjected to disciplinary action for dispensing illegitimate prescriptions for controlled substances. Most of these practitioners' registered locations were significant distances from [the pharmacy]." The pharmacy also filled multiple oxycodone and hydromorphone prescriptions for a customer who had previously abruptly left the pharmacy after learning the pharmacy personnel had suspected the customer of having a forged prescription.<sup>879</sup>

xxxii. On November 26, 2012, the DEA issued an OTSC to a Walgreens pharmacy in Fort Pierce, Florida.<sup>880</sup> The DEA also alleged this pharmacy "ignored readily identifiable red flags that controlled substances prescribed were being diverted and dispensed controlled substances despite unresolved red flags."<sup>881</sup> The red flags ignored by the pharmacy included "multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; and individuals paying for prescriptions for controlled substances with cash and non-insurance discount cards."<sup>882</sup>

xxxiii. On November 26, 2012, the DEA issued an OTSC to a Walgreens in Oviedo, Florida, alleging that it ignored red flags of "multiple patients coming with prescriptions for the same drugs in the same quantities coming from the same doctor; patients traveling long distances to the pharmacy; patients with the same address presenting substantially similar prescriptions; and, patients presenting combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam."<sup>883</sup>

xxxiv. In February 2013, the DEA served three more OTSCs on Walgreens pharmacies in Florida.<sup>884</sup> On February 4, 2013, the DEA issued an

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<sup>879</sup> *Id.* at -7709-7713.

<sup>880</sup> *Id.* at -7716-7719.

<sup>881</sup> *Id.*

<sup>882</sup> *Id.* at -7716-7719.

<sup>883</sup> *Id.* at -7722-7726.

<sup>884</sup> Press Release, DEA Serves Another Walgreens Pharmacy An Order To Show Cause, Drug Enforcement Administration (February 6, 2013), <https://www.dea.gov/press-releases/2013/02/06/dea-serves-another-walgreens-pharmacy-order-show-cause>;

OTSC to a Walgreens in Oviedo, Florida, alleging that it ignored red flags of “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and alprazolam; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; individuals paying for prescriptions for controlled substances with cash and non-insurance discount cards; individuals residing long distances from the pharmacy; and individuals residing long distances from the practitioners from whom the prescriptions were obtained.”<sup>885</sup>

xxxv. On February 11, 2013, the DEA served an OTSC to a Walgreens pharmacy in Fort Pierce, Florida, alleging it dispensed controlled substances despite red flags of “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same practitioner; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone and benzodiazepines; individuals presenting prescriptions for controlled substances issued by practitioners located long distances from the pharmacy; individuals presenting prescriptions for controlled substances issued by multiple practitioners, or ‘doctor shoppers’; and warnings documented by pharmacy employees regarding physicians prescribing illegitimately.”<sup>886</sup>

xxxvi. On February 19, 2013, DEA served an OTSC to a Walgreens pharmacy in Fort Meyers, Florida, alleging the pharmacy filled numerous controlled substance prescriptions despite customers exhibiting red flags including “multiple individuals presenting prescriptions for the same drugs in the same quantities from the same doctor; individuals with the same address presenting substantially similar prescriptions; individuals presenting prescriptions for combinations of controlled substances known to be highly abused, such as oxycodone, alprazolam and carisoprodol; individuals from out-of-state or who had travelled significant distances within state to fill prescriptions at [the pharmacy]; and filling new oxycodone prescriptions for customers when fewer than

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Press Release, DEA Serves An Order To Show Cause On Walgreen’s Pharmacy In Fort Pierce, Drug Enforcement Administration (February 12, 2013), <https://www.dea.gov/press-releases/2013/02/12/dea-serves-order-show-cause-walgreens-pharmacy-fort-pierce>;

Press Release, *DEA Serves An Order To Show Cause On Walgreen’s Pharmacy In Fort Myers*, Drug Enforcement Administration (February 22, 2013), <https://www.dea.gov/press-releases/2013/02/22/dea-serves-order-show-cause-walgreens-pharmacy-fort-myers>

<sup>885</sup> WAGMDL00387708 at -7729-7738

<sup>886</sup> *Id.* at -7740-7743.

30 days had elapsed since the customer had filled their previous prescription for a 30-day supply of oxycodone.”<sup>887</sup>

xxxvii. In June 2013, Walgreens entered into a three year Memorandum of Agreement with the Department of Justice and DEA that included \$80 million in civil penalties (the largest in DEA history at the time) to resolve the DEA’s administrative actions and investigation regarding the Florida distribution center and pharmacies.<sup>888</sup> The “Covered Conduct” encompassed by the Agreement included the failures to establish effective controls against diversion or report suspicious orders at the Distribution Center, as well as the pharmacies’ failure to exercise their “corresponding responsibility to ensure that controlled substances were dispensed pursuant to prescriptions issued for legitimate medical purposes by practitioners acting in the usual course of their professional practice, as required by 21 C.F.R §1306.04(a).”<sup>889</sup> The June 2013 agreement superseded the obligations of the 2011 Memorandum of Agreement,<sup>890</sup> and required Walgreens to “maintain a compliance program in an effort to detect and prevent diversion of controlled substances.”<sup>891</sup> Walgreens also committed to “continue to enhance its Good Faith Dispensing Policy and training materials to identify “red flags” of potential diversion for pharmacists to consider in making professional judgments regarding dispensing of controlled substances” and “train its pharmacy personnel at least annually on Good Faith Dispensing and will update the Good Faith Dispensing Policy and training materials to respond to changing diversion threats of which Walgreens is aware.”<sup>892</sup> By January 2013, Walgreens was aware that “this isn’t just a Florida problem”<sup>893</sup> and that “pharmacists are the front lines,” acknowledging that “the stores, on the one hand, and corporate headquarters, on the other hand, are best equipped to ensure compliance and assist in combatting controlled substance abuse.”<sup>894</sup>

xxxviii. Walgreens pharmacy managers were rewarded for increased prescription sales<sup>895</sup> and Walgreens included controlled substance

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<sup>887</sup> *Id.* at -7746-7751.

<sup>888</sup> WAGMDL00490963; *see also*: Press Release, U.S. Attorney’s Office S. Dist. of Fla., *Walgreens Agrees To Pay A Record Settlement Of \$80 Million For Civil Penalties Under The Controlled Substances Act* (June 11, 2013), <https://www.justice.gov/usao-sdfl/pr/walgreens-agrees-pay-record-settlement-80-million-civil-penalties-under-controlled>.

<sup>889</sup> WAGMDL00490963 at -0966.

<sup>890</sup> *Id.* at -0967, paragraph 3.

<sup>891</sup> *Id.* at -0968.

<sup>892</sup> *Id.* at -0977.

<sup>893</sup> WAGMDL00049752; WAGMDL00049753, at -9759.

<sup>894</sup> WAGMDL00659802, at -9807 and -9817.

<sup>895</sup> WAGFLDEA00000001 (“The best evidence of a well-run pharmacy is the increase in prescriptions and pharmacy sales.”)

prescription dispensing in bonus calculations for pharmacists and pharmacy technicians until 2014.<sup>896</sup> Despite removing controlled substances from the bonus calculations in 2014, Walgreens continued to incentivize speed in filling prescriptions and diminishing the time available to detect and resolve red flags, by using a metric of “Rx/day” to calculate bonuses.<sup>897</sup>, which inherently prioritized speed in filling prescriptions and reduced the time available to detect and resolve red flags.

- xxxix. A December 2014 audit performed after the 2013 DEA settlement found continuing supervision and compliance failures. The audit team found no formal monitoring program existed to confirm that pharmacies across the chain were complying with controlled substance documentation and retention requirements; no monitoring outside of the inadequate “Store Walk program” existed to monitor TD GFD requirements; and employees were failing to timely complete Good Faith Dispensing training, such that, at the time of the audit, over 35,000 employees had not completed their required training for that year.<sup>898</sup>
- xl. In June and July 2015, Walgreens performed an audit of a random sample of approximately 2,400 pharmacies to determine whether Walgreens was “compliant with the policies/procedures put in place” regarding dispensing pursuant to Walgreens’s agreement with the DEA.<sup>899</sup> As the audit progressed, Walgreens documents state that the audits were “not going great,” and that they would need to implement a “mitigation plan... to satisfy the MOA [Memorandum of Agreement]” for the non-compliance revealed by the audit.<sup>900</sup> Walgreens concluded that the audit “Results were unfavorable.”<sup>901</sup> Fewer than 60% of stores were in compliance with TD GFD for filled prescriptions; 1,160 stores did not have a single refused prescription in a nine month period,<sup>902</sup> an indicator that prescriptions were undoubtedly dispensed despite unresolved red flags.
- xli. Even with sporadic Targeted Drug Good Faith Dispensing compliance, Walgreens projected a \$65 million “DEA Financial Impact”<sup>903</sup> with the largest dispensing declines in the three TD GFD drugs (oxycodone,

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<sup>896</sup> WAGMDL00490963

<sup>897</sup> FY19 Business Planning – Pharmacy & Retail Operations; WAGMDL00706531.

<sup>898</sup> WAGMDL00674321

<sup>899</sup> WAGMDL00037616 at slide 3; WAGFLAG00092402 (RXI June BCI questions with sources)

<sup>900</sup> WAGMDL00045962

<sup>901</sup> WAGMDL00037616 at -7618; *See also* WAGMDL00487576

<sup>902</sup> WAGMDL00037616

<sup>903</sup> WAGMDL00015233

hydromorphone and methadone).<sup>904</sup> A later 2015 overview of “Good Faith Dispensing” training materials noted an increase in customer complaints and “a decline in dispensed controlled substance prescriptions over recent years” emphasizing that “Good Faith Dispensing Training is intended to *increase patient retention, decrease customer complaints* and for pharmacists to continue dispensing legitimate controlled substances to legitimate patients for a valid medical purpose.”<sup>905</sup>

- xlii. Failure to prevent inappropriate dispensing likely occurred, in part, due to Walgreens’ imposition of “performance metrics,” as discussed below. In short, performance metrics assess whether pharmacists are meeting goals that are largely driven by profits and numbers of prescriptions filled. For example, in February 2012, Richard Ashworth, then the Vice President of Walgreens’ Western Division, supervising over 2,000 Walgreens stores, encouraged stores “to drive for the activities that drive incremental scripts. There are metrics we can improve, today, that we will demonstrate the ‘doing whatever it takes’ to achieve 100% of FY2011 Script volume,” noting “we are not doing whatever it takes,” and particularly that in the “Top 2 complaints” was “Pharmacy Fill was denied.”<sup>906</sup> In 2013/2014, these types of customer complaints impacted pharmacy manager compensation directly since 25% of their bonus calculation was based on “customer delight.”<sup>907</sup> Customer complaints regarding refusal or time to dispense TD-GFD prescriptions would be factored into “customer delight” calculations and impact manager compensation.
- xlili. Walgreens’ internal documents show the stress and strain reported by employees due to the imposition of such metrics. A March 2013 document outlining Pharmacy Managers’ feedback on current challenges stated that pharmacists did not have enough time to do the multiple tasks assigned to them, and that a lack of resources kept them from being effective and consistent.<sup>908</sup> Pharmacy managers also stated that they were “[s]truggling to keep our heads above water *let alone* manage.”<sup>909</sup>
- xliv. Rx Supervisor Workload Feedback notes dated May 24, 2013, stated that Pharmacy Supervisors spend as much as 3-4 hours/week answering complaints related to Good Faith Dispensing, which impacted time

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<sup>904</sup> WAGMDL00015230, at -5232.

<sup>905</sup> WAGMDL00656379 (emphasis added)

<sup>906</sup> WAGMDL00974032

<sup>907</sup> WAGMDL00706302, at -6302 and -6305.

<sup>908</sup> WAGMDL01166994

<sup>909</sup> *Id.*



spent performing any other responsibilities.<sup>910</sup> The notes also stated that some stores were responsible for making an unrealistic amount of patient calls, sometimes over 100 phone calls per day.<sup>911</sup> Those notes went on to point out that pharmacy supervisors had been asked to visit hospitals to suggest Bedside Delivery and that “[a]ll RXS on the call felt that tasks are continually being added to their plate and no activities are being taken away. It makes it extremely tough to manage these new tasks in addition to store walks and other daily responsibilities.”<sup>912</sup>

- xlvi. In late 2016, Walgreens pharmacy manager Malwina Sarnas reported “feeling pressured by both her store MGR [manager] and DM [district manager] to fill prescriptions she is not comfortable filling” after customer complaints resulting from a refusal to fill target drug GFD prescriptions with unresolvable red flags, including early refills, cash payments and customers residing long distances from the pharmacy location.<sup>913</sup> Ms. Sarnas was reassured that “You should not feel compelled to fill (or refuse) prescriptions solely based on comments made by management” but in fact, as discussed above, pharmacy manager compensation was based in part on performance metrics including “customer delight” and the achievement of sales and profit goals.
- xlvi. In December 2016, the Chicago Tribune reported that Walgreens pharmacists, when filling prescriptions, missed approximately 1 in 3 (30%) of drug interactions, dispensing medication without warning patients of the risk of potentially dangerous or even fatal side effects of the co-prescribed drugs.<sup>914</sup> The investigation found that “pharmacists frequently race through legally required drug safety checks, including whether the dose is reasonable and whether the medication might interact with other drugs the patient is taking.” In response to the article, Walgreens admitted it collects business metrics to monitor staffing levels and service, but denied using them “in a manner that emphasizes productivity over patient safety.” Walgreens “said it would provide additional training on drug interactions” for its pharmacists and would work to move “administrative tasks out of stores and to a centralized office” to “give pharmacists more time to help patients.”<sup>915</sup> While some pharmacists did properly warn, “in test after test, other

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<sup>910</sup> WAGMDL01166882

<sup>911</sup> *Id.*

<sup>912</sup> *Id.*

<sup>913</sup> WAGMDL00093658

<sup>914</sup> WAGNMAG00009844 at WAGNMAG00009850; Sam Roe *et al.*, Pharmacies Miss Half of Dangerous Drug Combinations, Chi. Tribune (Dec. 15, 2016), <https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html>

<sup>915</sup> *Id.*



pharmacists dispensed dangerous drug pairs at a fast-food pace, with little attention paid to customers. They failed to catch combinations that could trigger a stroke, result in kidney failure, deprive the body of oxygen or lead to unexpected pregnancy with a risk of birth defects.”<sup>916</sup> The Tribune reporters said that their 2-year study “exposes fundamental flaws in the pharmacy industry. Safety laws are not being followed, computer alert systems designed to flag drug interactions either don’t work or are ignored, and some pharmacies emphasize fast service over patient safety. Several chain pharmacists, in interviews, described assembly-line conditions in which staff hurried to fill hundreds of prescriptions a day.”<sup>917</sup>

- xlvi. Walgreens internally discussed the testing used by the investigation and the report.<sup>918</sup> In each instance, the drug interaction should have triggered a “Major DUR [Drug Utilization Review].” While none of the tests were for a “cocktail drug” combination (i.e. opioids plus another problematic controlled substance), the Major DUR was the same internal red flag mechanism used by Walgreens for flagging cocktail drugs. For the Tribune investigation, a pharmacy “passed” the test if the pharmacist *either* called the doctor *or* counseled the patient when presented with the drug combination.<sup>919</sup> Walgreens “passed” 19 out of 30 tests.
- xlvi. Walgreens also internally discussed that, in response to the report, Carmen Catizone, executive director of the National Association of Boards of Pharmacy, previously told the Tribune he would like to see all states require pharmacists to provide counseling about first-time medications and changes of doses. Catizone also said authorities should examine whether to set minimum staffing levels for pharmacies to address workload issues. Pharmacies sometimes have to fill hundreds of prescriptions a day. Catizone said he wanted states to publicly disclose pharmacy medication errors, and that authorities should examine whether to set minimum staffing levels for pharmacies to address workload issues.<sup>920</sup>
- xli. On February 16, 2018, Walgreens pharmacist Robert Jaeger wrote an email to inform Walgreens that store managers had challenged and attempted to override his “refusal to fill a prescription for a C2 medication,” and that such conduct was part of a larger problem.<sup>921</sup> In my opinion, Mr. Jaeger’s account calls into serious question the “Good

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<sup>916</sup> *Id.*

<sup>917</sup> Sam Roe *et al.*, Pharmacies Miss Half of Dangerous Drug Combinations, Chi. Tribune (Dec. 15, 2016), <https://www.chicagotribune.com/investigations/ct-drug-interactions-pharmacy-met-20161214-story.html>.

<sup>918</sup> WAGMDL00250895

<sup>919</sup> WAGMDL00250895 at slide 3

<sup>920</sup> *Id.* at slide 4, speakers notes

<sup>921</sup> WAGCASF00046090, at -6096 (emphasis in original)

Faith” in Walgreens’ “Good Faith Dispensing,” and highlights, instead, the inherent conflict between profit and pleasing customers, on the one hand, and the “corresponding responsibility” to fill only prescriptions for a legitimate medical purpose, on the other. I agree with Mr. Jaeger’s conclusion that this conflict results in filling of illegitimate prescriptions that have contributed to the opioid epidemic. Salient portions of Mr. Jaeger’s detailed account are excerpted below:

- A. On January 15, 2018, Mr. Jaeger refused to fill a prescription for a C-II medication, following the Walgreens policy regarding “good faith dispensing.” One of the red flags Mr. Jaeger identified was that “the patient threatened me.” The customer was upset and “made numerous complaints to the company.” A number of store managers were at Mr. Jaeger’s store for a meeting that day. Two of the managers from other stores challenged Mr. Jaeger’s decision, stating, “if the prescription is not being filled early and the dose is within safe limits, you cannot not refuse to fill the prescription,” and denying that the customer’s behavior could be a cause not to dispense. According to Mr. Jaeger’s complaint, he was told that “a store manager representing the Walgreens Company and my superior, is the authority in cases of determining when to fill prescriptions for controlled substances including opiates.” He described the managers’ behavior as “extremely intimidating and persuasive.” Mr. Jaeger informed the managers that the customer had threatened to call his supervisor, and that DEA guidance included assertive and abusive behavior as a red flag. The managers disagreed and stated that customer behavior was not considered in the GFD policy.
- B. Mr. Jaeger’s email noted the conflict between managers wanting to avoid complaints that affect their bonuses, and the need to follow the law, stating, *“As long as Walgreens allows their pharmacists to be evaluated by store managers (who are trained by the Company to be concerned with profit, customer service, and resolving customer complaints), store managers will assert their authority over the pharmacists and will naturally confuse good faith dispensing issues with customer service issues. This is a clear conflict of interest.”*
- C. Mr. Jaeger continued, “please do not mistake this as an isolated event and treat it as such. I have now recently had 3 store managers, a district manager, and a pharmacy supervisor lay down resistance when I refused to fill a prescription. I was even threatened with being insubordinate when I resisted. I also know many other pharmacists, both currently working for

the Company and others who have since left, who have felt the same pressure, either by being directly told or to have resistance placed on them, to fill prescriptions that went against their own professional judgment. All pharmacists were also given training at the district office to offer guidance on good faith dispensing. Some who led the discussion were not even pharmacists, but rather were people in a position of authority who also perceive personal gain and profit for the Company if the pharmacists continue to fill controlled substances without questioning their legitimacy. The take home message of the meeting was to lean more toward dispensing and not refusing to fill prescriptions for controlled substances. Let me point out that during the meeting there were several scenarios that were given in which a prescription for a controlled substance was brought into the pharmacy. Some scenarios had ‘red flags.’ In all but one scenario it was concluded by the people conducting the meeting that we should just go ahead and fill the prescription.”

- D. Mr. Jaeger documented other troubling incidents of a similar nature: “The other day I refused to fill a controlled prescription for a patient for obvious multiple red flags. I made documentation and I flagged the patient’s profile so as to prevent other Walgreens pharmacies from filling it. I even told the patient his prescription would not be welcomed by any Walgreens. It got filled anyway at a Walgreens pharmacy, against company policy.”
- E. Mr. Jaeger’s email concluded, “This was not handled correctly the first time I brought it to the attention of the Company. Although I received an apology, the reality is that nothing has changed and the problem inherent in the system was not corrected. It was treated as an isolated incident. *It is my expectation that Walgreens Boots Alliance, Inc. upholds its own policies and adheres to its Code of Conduct and Business Ethics and does the right thing by correcting this conflict of interest because it directly contributes to the diversion of controlled substances and to the deaths of tens of thousands of Americans from drug overdose abusing dangerous prescription drugs. How many of these deaths can be accounted for by controlled substances furnished at a Walgreens Pharmacy?*”
- I. In June 2018, when a pharmacy manager raised concerns regarding “consistently seeing high amount of opioids also combined with benzodiazepines” from a doctor who “also seems to be in the fashion of pre-writing ‘diagnosis’ codes on his scripts, as if to discourage phone

calls/questions to his office, as mostly likely many pharmacies feel his scripts are questionable”, the manager was informed that “we cannot ‘blanketly’ refuse or systematically deny his prescriptions” and was further told to “advise pharmacy staff to refrain from entering any slanderous comments in the prescribers IC+ profile”.<sup>922</sup> In fact, Walgreens was able to track internal data on “top risk Prescribers, Patients and Pharmacists”<sup>923</sup> and could and did ‘blanketly’ refuse prescribers as part of a pilot program in 2013 which allowed for “prescriber sanctioning where we identified high prescribing physicians over select controlled substances as compared to their peers” leading to Walgreens refusing to accept controlled substance prescriptions written by at least 8 prescribers.<sup>924</sup>

- li. In approximately December 2019, Walgreens retained Tata Consulting Services (TCS), to look into a number of Walgreens’ issues, including stress levels among pharmacists. In or around December 2019, Tata Consulting Services (TCS) performed an analysis of certain issues related to Walgreens’s pharmacies, including stress levels among pharmacists. As reported by the New York Times in February 2020:<sup>925</sup> “Pharmacy employees at Walgreens told consultants late last year that high levels of stress and ‘unreasonable’ expectations had led them to make mistakes while filling prescriptions and to ignore some safety procedures. But when the consultants presented their findings at Walgreens’s corporate offices this month, there was no reference to the errors and little mention of other concerns the employees had raised. That’s because senior leaders at Walgreens had directed the consultants to remove some damaging findings after seeing a draft of their presentation, a review of internal emails, chat logs and two versions of the report shows. In one instance, Amy Bixler, the director of pharmacy and retail operations at Walgreens, told them to delete a bullet point last month that mentioned how employees ‘sometimes skirted or completely ignored’ proper procedures to meet corporate metrics, according to the chat logs and the draft report. A slide detailing ‘errors resulting from stress’ was also removed. The consultants, a group from Tata Consultancy Services that was examining the company’s computer system for filling prescriptions, had included the slide among their ‘high level findings.’ ... The pharmacy chains have pushed back on the complaints, saying staffing was sufficient and errors were rare. Walgreens told The Times that its pharmacists knew ‘they should never work beyond what they believe is advisable.’ But the consultants heard similar complaints in interviews with workers at eight Walgreens

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<sup>922</sup> WAGMDL00091654.

<sup>923</sup> WAGMDL00095578.

<sup>924</sup> WAGMDL01013472, at -3479-3480.

<sup>925</sup> Gabler, E. “How Chaos At Chain Pharmacies Is Putting Patients at Risk.” New York Times (January 31, 2020). <https://www.nytimes.com/2020/01/31/health/pharmacists-medication-errors.html>

pharmacies last year. Both versions of the consultants' report noted 'a widespread perception that there is not enough time to respond to all pharmacy tasks.' In the deleted slide on stress-related errors, the consultants wrote, 'We were told that pill bottles had been found to contain more than one medication.' They said they 'heard multiple reports of improper behavior that was 'largely attributed to the desire' to meet a corporate metric known as 'promise time,' which ensures that patients get prescriptions filled within a set amount of time. The Times reported last month that such metrics often factor into employee bonuses and performance reviews. The final presentation was delivered about two weeks ago at the drugstore chain's corporate campus in Deerfield, Ill. The consultants had been seeking approval of the research report from various departments at Walgreens. They have since moved to the next step in the project — improving the pharmacy's computer system.

- lii. Early drafts of the Tata presentations include slides with troublesome findings, some of which were included in later drafts, but some of which were deleted or significantly softened at Walgreens's request.<sup>926</sup> Tata employees noted that some of the requests to remove information from slides conflicted with their business ethics.<sup>927</sup> Below are some of the more significant slides from version 3 of the report:<sup>928</sup>

**HIGH VARIATION IN PERCEPTION OF PHARMACY EFFICIENCY**

**Significant gaps in trust**

- There was widespread mistrust of inventory numbers both when reported by the system and other staff members
- A majority of Pharmacists we spoke with thought they understood laws and regulations better than the system
  - The Pharmacy Managers suggested that such confidence was misplaced and that it is easy for misunderstandings to spread and persist in individual pharmacies
- It was reported that improper overrides for coupons occurred because users did not trust the system to properly process coupons and trusted their understanding of the coupons system more
- Users reported that they felt their coworkers were less capable or knowledgeable than them, with the exception of new hires
  - This was true markedly true between more senior Technicians and Pharmacists, with Technicians suggesting that they are more important to keeping the pharmacies running and Pharmacists suggesting that they have to cover for Technician errors

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<sup>926</sup> WAGMDL01109276

<sup>927</sup> *Id.*

<sup>928</sup> See TCS00000196 (Version 3) as compared to TCS00000396 (Version Six)



**HIGH STRESS****Errors resulting from stress**

- We heard multiple reports of improper behavior which was largely attributed to the desire to keep below promise time
  - We were told that pill bottles had been found to contain more than one medication
  - We also heard that prescriptions returned to the shelf were sometimes poured back into the stock bottles, including one instance of this occurring with a liquid medication
- All participants expressed a high level of stress in trying to meet promise time and the belief that, given current levels of staffing, promise time was unreasonable while following proper procedure
  - Two participants claimed that they don't believe that the corporate teams care for them and are too focused on promise time
    - One said that they are concerned about taking their lunch break as they feel they are judged for not making promise time following the lunch break and cut their break short

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**USER PERCEPTIONS****Users are typically responsive instead of proactive**

- There is a widespread perception that there is not enough time to respond to all pharmacy tasks
  - Proper procedures are sometimes skirted or completely ignored due to worries of meeting promise time
    - These can be as serious as returning medication to stock bottle instead of properly restocking
- Users prioritize task comfort due to the perception that engaging in new or unfamiliar tasks will drag down pharmacy performance
  - In the long term this reduces user skill and significantly impacts pharmacy efficiency
- Unusual task load or unexpected changes in the pharmacy environment are very disruptive to less efficient pharmacies
  - Not enough buffer time to accommodate such changes

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### USER PERCEPTIONS

**Users believe that corporate doesn't understand their needs**

- When there is not a strong leadership voice users think that corporate expectations are impossible to achieve
  - Promise time is thought to be unreasonable given necessary tasks
  - Training is seen as insufficient prior to working in the pharmacy
  - Users expect that turnover is unsustainable given then learning curve of new Technicians
- Users feel that the issues with IC Plus and Core Workflow should be obvious and easy to solve
  - Hard separation of information across windows, tabs, and Store Net is seen as arbitrary and unnecessary
- Many tasks, such as responding to patient calls, are seen as a waste of time that should be handled in other ways

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### TRAINING GAP

**Current training is seen as insufficient by new users and managers**

- Users expressed that current training does not prepare them for actually working in the pharmacy
- The need to have employees quickly onboarded results in rushed and incomplete training
- Current training is not seen as 'hands on' enough and does not present realistic system usage
- Users estimate it takes 5-7 months after initial training is supposed to be completed before developing full competency
- Senior Technicians and Pharmacy Managers feel that they become de facto teachers to new Technicians which is major burden on them and a drag on pharmacy efficiency
- There is a large deficit in user guidance within the current design which could bridge this training gap

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1. Defendant Walmart lacked effective controls and actively undermined efforts of pharmacists to prevent diversion.
  - i. In November 2005, Walmart adopted Section 1703 of its Pharmacy Operations Manual (POM) which included instructions for handling



suspected forged or altered prescriptions, such as contacting the prescribing physician for verification, and contacting local authorities as recommended by the DEA. This POM provision did not mention concerns over diversion or risks to customers from drug combinations or “cocktails,” did not address prescriber characteristics such as high doses or frequent prescribing, and did not provide information about indicators of suspected diversion or prescribing outside the scope of legitimate medical purpose.<sup>929</sup> As such, the 2005 version of Section 1703 was inadequate to the task of instructing pharmacists on detection and resolving red flags before dispensing prescription opioids.

- ii. In August 2007, three months after the news of Purdue’s guilty plea, Walmart issued an update to Section 1703 of the POM, which added a section entitled, “Potential Indicators of Fraudulent, Forged or Altered Prescriptions.” This section advised to “Watch for unusually high quantities and/or dosages,” customers unwilling to bill to their insurance, and indicators of fraud on the face of the prescription, such as different colors of ink or different handwriting. The 2007 POM did not mention concerns over patients traveling long distances, high volume prescribers (pill mills), diversion or risks to customers from drug combinations or “cocktails,”<sup>930</sup> although DEA had begun enforcement actions prior to that time on the basis of pharmacies dispensing in spite of such concerns.
- iii. The April 2009 version of POM 1703 included the introductory statement, “This policy provides guidance on how to identify and handle forged or altered prescriptions in order to comply with State and Federal requirements, detect and prevent diversion, protect the safety of our associates and patients, and ensure that reasonable grounds exist to refer forged and/or altered prescriptions to law enforcement.”<sup>931</sup> The POM then listed factors suggested by the DEA that may be “indicators of forged or altered prescriptions,” including, “Unusually high quantities and/or dosages that differ from usual medical use,” and “Multiple patients appearing in a short period of time bearing similar prescriptions from the same physician.”<sup>932</sup>
- iv. This POM reference to “unusually high quantities” and “multiple prescriptions from the same physician” appears to relate to the pill mill problem. However, this belated measure did not correct Walmart’s actual practice. As documented in the December 2020 Complaint of the Department of Justice (DOJ), Walmart ignored repeated pleas from its pharmacists to refuse to fill opioid prescriptions from known pill mills. In fact, over the course of 44 pages, the Complaint provides details of

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<sup>929</sup> WMT\_MDL\_000069188

<sup>930</sup> WMT\_MDL\_000069223

<sup>931</sup> WMT\_MDL\_000069228

<sup>932</sup> *Id.*

“20 examples of the numerous prescribers whose *egregious and unprofessional prescribing practices were known to Walmart*. The examples are organized in alphabetical order by the prescribers’ initials. In each example, Walmart pharmacists repeatedly recognized, and reported to Walmart’s compliance unit, that a particular prescriber was issuing prescriptions without a legitimate medical purpose or outside the usual course of professional practice. In each example, *Walmart’s compliance unit knew that its pharmacists were continuing to be presented with prescriptions issued by those prescribers, and that, based on the reported red flags, there was a very high probability that the prescribers were regularly issuing invalid controlled-substance prescriptions.*”<sup>933</sup> These examples included a Florida physician whose “patients” filled his prescriptions at Walmart stores in 32 states around the country, including Ohio, as well as dispensing violations at Walmart stores in Arkansas, Colorado, Delaware, Ohio, Georgia, Indiana, North Carolina, Pennsylvania, Texas, and Wisconsin.<sup>934</sup> In short, there were nationwide CSA violations throughout Walmart’s system.

- v. In February 2009, Walmart POM 1311, to which POM 1703 referred, stated Walmart’s “uniform national policy” to determine whether a proper prescriber-patient relationship exists, and provided a list of indicators, including prescribers outside the US or out-of-state; prescriptions outside the scope of customary practice; prescribers known to be retired or deceased; “the prescription is for a large quantity (especially controlled substances),” and “the prescription is for a large number of a particular strength.”<sup>935</sup> A similar list appeared in the March 2011 version of POM 1311.<sup>936</sup>
- vi. While the POM 1703 and 1311 provisions of 2009 and 2011 cite DEA guidance as their source, those provisions omit numerous red flags of potentially illegitimate prescribing that had been the subject of prior DEA enforcement actions, which went well beyond the scope of “forged or altered prescriptions,” including traveling significant distances from one’s residence to a pharmacy; paying in cash; and drug combinations, or “cocktails,” consisting of either an opioid (such as oxycodone) plus a benzodiazepine (such as alprazolam), or a “trinity” consisting of those two drug categories with the addition of a muscle relaxant (such as carisoprodol). These red flags were identified in the

<sup>933</sup> Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 50-94, paragraphs 176-356 (emphasis added).

<sup>934</sup> *Id.*, at paragraph 302.

<sup>935</sup> WMT\_MDL\_000069108 at 69109.

<sup>936</sup> WMT\_IN\_AG\_00000066 at 00000067.

*East Main Street* case, which was filed in April 2009, based on conduct that had occurred in 2005-2006, and decided in 2010 in a published order.<sup>937</sup>

- i. The absence of red flags for opioids + benzodiazepines, and for the trinity of those two drugs plus a muscle relaxant, is a significant omission that failed to properly instruct Walmart's pharmacists as to both the potential for diversion, since the drugs were known to increase the high among drug users, and the increased risks of medical complications, especially the synergistic effects on respiratory depression, which were known to increase the risk of overdose and death well before 2009.<sup>938</sup>
- ii. Despite the acknowledgment of large prescribed quantities of opioids as warning signs in the 2009 and 2011 versions of POM 1311, Walmart's actions did not match the policy. Instead, "During the Dispensing Violations Period, from June 26, 2013, to the present,<sup>939</sup> *Walmart violated the CSA's dispensing rules on a sweeping national scale, filling enormous numbers of invalid controlled-substance prescriptions.*"<sup>940</sup>
- iii. Following an enforcement proceeding where DEA accused Walmart of violating its dispensing violations, in March 2011, "DEA and Walmart entered into a nationwide memorandum of agreement ("MOA") to resolve an administrative action predicated upon a California Walmart pharmacy's alleged failure to comply with its dispensing obligations when filling controlled substance prescriptions, including filling such prescriptions where the prescription was not issued for a legitimate medical purpose or by a prescriber acting within the usual course of professional practice. The MOA was in effect from March 2011 through March 2015. In the MOA, Walmart committed to, among other things, 'maintain a compliance program, updated as necessary, designed to detect and prevent diversion of controlled substances as required by the Controlled Substances Act.'"<sup>941</sup>

<sup>937</sup> *East Main Street Pharmacy*; Affirmance of Suspension Order, 75 Fed. Reg. 66,149 (Oct. 27, 2010).

<sup>938</sup> See summary of opioid + benzodiazepine medical literature, above, at Section §C.6.j. *See, e.g.,* Jones, et al., Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012 September 1; 125(1-2): 8–18. doi:10.1016/j.drugalcdep.2012.07.004.

<sup>939</sup> The "present" would mean December 20, 2020, when the Complaint was filed.

<sup>940</sup> Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p.29, paragraph 105. (emphasis added.)

<sup>941</sup> *Id.*, at pp.40-41, paragraphs 136-137.

- iv. While the MOA demonstrates Walmart's explicit knowledge of the problem of opioid diversion, the MOA did not result in Walmart's compliance with the CSA; instead, prescriptions from pill mill doctors continued: "Even when pharmacists determined by themselves that prescribers were acting as pill mills, Walmart's compliance unit refused to let the pharmacists categorically refuse to fill all prescriptions issued by such prescribers. Rather, the compliance unit told pharmacists that they needed to consider each individual prescription—an approach that made it impractical for pharmacists to reject all prescriptions issued by these pill-mill prescribers, particularly given the strict time pressures Walmart imposed on its pharmacists for filling prescriptions."<sup>942</sup> The "enormous" CSA violations were ongoing, as documented in the DOJ Complaint. In 2012, Walmart adopted a policy *requiring* that its pharmacists conduct a PDMP check for every request to dispense oxycodone immediate release 30 mg, because it had been identified "through careful analysis as a highly prescribed medication with high abuse potential."<sup>943</sup> This requirement eventually was incorporated into Walmart's POM 1316, in April 2016.<sup>944</sup> In my opinion, Walmart could have and should have required that its pharmacists conduct a PDMP check for *all* opioids, not just oxycodone 30 mg, and that requirement should have been stated consistently in its POMs.
- v. In January 2013, Walmart replied to NACDS' list of proposed red flags, discussed above, and suggested responses by the pharmacy and pharmacists. Walmart disagreed with many of the NACDS proposals, including identifying a red flag for "Excessive volume and rate of growth of dispensing controlled substances."<sup>945</sup> This is a telling disagreement, in light of the misconduct described in the DOJ Complaint, highlighting Walmart's history of filling "enormous" quantities of controlled substance prescriptions, which would necessarily have contributed to "excessive volume and rate of growth" of such dispensing. Walmart's own data on prescription opioid sales, mandated to be kept by the CSA,<sup>946</sup> would have provided Walmart with the data to analyze this red flag, which it could and should have done, but did not do.
- vi. As to NACDS' proposed action of removing controlled substances from dispensing incentive programs, Walmart's response stated, "Incentive programs should be entirely agnostic as to the type of prescriptions (controlled substances or non-controlled drugs) filled."<sup>947</sup>

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<sup>942</sup> *Id.*, at p. 48, paragraph 166.

<sup>943</sup> WMT\_MDL\_000069746.

<sup>944</sup> WMT\_MDL\_000043015

<sup>945</sup> WMT\_MDL\_000891159 at 1175-1176.

<sup>946</sup> Deposition of Demetra Ashley, In re: National Prescription Opiate Litigation (MDL No. 2804, Case No. 17-md-2804), March 11, 2021, 132:14-134:17.

<sup>947</sup> WMT\_MDL\_000891159, at 1175.

In other words, Walmart's position *included controlled substances in programs that incentivized their sale*. This policy inappropriately encouraged the sale of addictive drugs, and made it more likely that consumers would be exposed to their dangers. In particular, an incentivized dispensing program rewards speed and efficiency, which may be appropriate for low-risk drugs, but those values are contrary to the vigilance and diligent investigation required as to prescriptions for controlled substances, especially during an epidemic of diversion and overdose mortality. The DOJ Complaint documents the pattern of inappropriate time pressures to fill prescriptions rapidly, and the concerns of pharmacists that speed did not allow for diligent investigation.<sup>948</sup>

- vii. Walmart's Pharmacy Facility Incentive Plan for 2012 provided for bonus payments based on numbers of prescriptions, amount of profits, and customer relations, compared to established benchmarks. The program was designed "to reward our associates if pre-defined business goals are met or exceeded."<sup>949</sup> As numbers of scripts went up, and as profits went up, incentive payments increased. A Management Incentive Plan (MIP) bonus provided for additional payments to all eligible associates based on the extent to which the number of annual prescriptions exceeded 190,000.<sup>950</sup> The Incentive Plan made no mention of patient safety goals, nor red flag detection goals. For as long as such programs were in place, they contradicted the need for effective controls against diversion, instead emphasizing speed and profits.
- viii. As to the mandatory use of the PDMP included in the NACDS red flag document, Walmart responded, "If the pharmacist has reason to believe that the prescription has not been issued for a legitimate medical purpose, tools such as PDMP should be utilized."<sup>951</sup> Walmart's response regarding the PDMP mirrored its POM 1316, which pertained to use of Prescription Monitoring Programs, or PMPs. The March 2011 and August 2012 versions of POM 1316 advised Walmart pharmacists that the use of a PDMP was permissive, not mandatory, and would only be used if the pharmacist believed, in the exercise of professional judgment, that the use of the PDMP would be helpful in determining

<sup>948</sup> See Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>. at p. 6, paragraph 6: "Walmart made it difficult for its pharmacists to follow the rules. Walmart managers put enormous pressure on pharmacists to fill prescriptions—requiring pharmacists to process a high volume of prescriptions as fast as possible, while at the same time denying them the authority to categorically refuse to fill prescriptions issued by prescribers the pharmacists knew were continually issuing invalid prescriptions."

<sup>949</sup> WMT\_MDL\_000043526, at 43528.

<sup>950</sup> *Id.*, at 43528-535.

<sup>951</sup> WMT\_MDL\_000891159 at 1177.

whether a prescription was legitimate.<sup>952</sup> But the use of the PDMP is to assist in making the determination of legitimacy in the first place. Particularly in the face of an ongoing epidemic of prescription opioid overdose mortality, the mandatory use of the PDMP would have provided essential information to prevent excessive prescribing of opioids alone, and of opioid cocktails with other drugs that increase likelihood of diversion and severe medical complications.

- ix. On August 7, 2013, an internal Walmart email from C. Scott Ortolani, RPh and Walmart Market Director, to Brad Nelson, stated the “inspectors collectively feel Walmart is [s]tarting to become a ‘funnel’ with C-II’s due to more liberal policies on dispensing pain meds.”<sup>953</sup> This is consistent with, and supportive of, the facts alleged in the DOJ complaint of December 2020.
- x. Based on my review of Walmart’s chronology of POMs, a red flag for “cocktails” of “commonly abused drugs” or drug combinations that could cause “medical complications” ultimately appeared in the July 2015 version of POM 1311.<sup>954</sup> The inclusion of this provision in 2015 supports my opinion that Walmart believed it was proper to instruct its pharmacists to be aware of the risks of diversion and medical complications presented by drug cocktails, and my further opinion that it was improper to omit those red flag instructions to pharmacists for a period of years prior to July 2015.
- xi. Despite the lack of a comprehensive list of red flags in the Walmart POMs, it appears from the DOJ Complaint that at least some Walmart pharmacists were aware of the red flags for “cocktail” prescribing, and that they brought those concerns to their supervisors, yet Walmart continued to fill such prescriptions without regard for obvious risks of diversion and serious medical complications or death. For example, according to the DOJ Complaint, “[f]rom June 26, 2013, through January 2017, despite Walmart’s knowledge of red flags indicating a very high probability that [physician] F.B. regularly issued invalid prescriptions for controlled substances, Walmart filled more than 500 controlled-substance prescriptions written by F.B. for Medicare patients.” Over 200 of those prescriptions were for Schedule II controlled substances, including “cocktails” of Percocet [opioid plus

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<sup>952</sup> WMT\_MDL\_000069142; WMT\_MDL\_000069148. (Note that Walmart’s term, “PMP,” has the same meaning as the term “Prescription Drug Monitoring Program,” or PDMP, as used by the NACDS and elsewhere.)

<sup>953</sup> WMT\_MDL\_000649191

<sup>954</sup> WMT\_IN\_AG\_00000079 at 00080. (Note that the first page of the document states a date of “June 2105,” while the remaining pages all state “July 2015.”)



acetaminophen], Xanax [benzodiazepine], Adderall (stimulant) and sometimes Soma [muscle relaxant].<sup>955</sup>

- xii. The December 2016 and January 2017 versions of Walmart POM 1311 included text as to red flags for “cocktails” that was identical to the provisions of the July 2015 version of POM 1311.<sup>956</sup> However, beginning in February 2017, the red flag for “cocktails” added the qualifier, “(i.e. an opioid, a benzodiazepine, and a muscle relaxant). This is often referred to as the ‘trinity’ or ‘holy trinity.’”<sup>957</sup> This change was ill-advised, since it specified to the pharmacist that the only cocktail to be concerned about must have included all three drugs. That is contrary to the medical literature, which identifies opioids + benzodiazepines as a high-risk combination, and also to DEA precedent, which identified the risks of both diversion and medical complications in earlier decisions as to the opioids + benzodiazepines combination, regardless of the presence of any other drug. The June 2017 version of POM 1311 lists the same set of red flags that listed the “trinity” of opioids + benzodiazepines + muscle relaxant, but did not identify opioids + benzodiazepines (without the third drug), as a red flag.<sup>958</sup>
- xiii. Under the circumstance of Walmart’s egregious disregard for red flags of all kinds, including prescription of known “cocktails” that increase the high while also increasing the likelihood of overdose mortality, the question of whether the written policy included a red flag only for the “trinity” may seem to be of relatively minor importance. However, given that Walmart has more than 5,000 pharmacies that dispense prescription opioids and other controlled substances, and that each pharmacy employs multiple pharmacists, all of whom were required to be familiar with the POM and its provisions, accurate and appropriate POM policies to identify red flags would have informed all pharmacists of the need to investigate prescriptions for opioids in combination with benzodiazepines that were dispensed at Walmart stores. Those prescriptions should have been subjected to a red flag investigation to determine whether they were issued for a legitimate medical purpose or posed a risk of diversion. It is reasonable to conclude that a substantial number of such prescriptions were illegitimate, in light of the known facts of drug-seeking use of that combination.
- xiv. As part of my work in this case, I have reviewed substantial investigative reporting, including interviews with Walmart pharmacists,

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<sup>955</sup> Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, p. 55, paragraphs 190-191.

<sup>956</sup> WMT\_IN\_AG\_00000084 at 0085.

<sup>957</sup> WMT\_IN\_AG\_00000118 at 0119.

<sup>958</sup> WMT\_NH\_AG\_00000124

that reinforces the allegations of the DOJ 2020 Complaint, including a lengthy article published by Pro Publica on March 25, 2020, which summarized the key findings of a DOJ investigation as follows: “Opioids dispensed by Walmart pharmacies in Texas had killed customers who had overdosed. The pharmacists who dispensed those opioids had told the company they didn’t want to fill the prescriptions because they were coming from doctors who were running pill mills. They pleaded for help and guidance from Walmart’s corporate office. Investigators had obtained records of similar cries for help from Walmart pharmacists all over the country: from Maine, North Carolina, Kansas and Washington, and other states. They reported hundreds of thousands of suspicious or inappropriate opioid prescriptions. One Walmart employee warned about a Florida doctor who had a list of patients from Kentucky that have been visiting pharmacies in all of central Wisconsin recently.’ That doctor had sent patients to Walmarts in more than 30 other states. In response to these alarms, Walmart compliance officials did not take corporate-wide action to halt the flow of opioids. Instead, they repeatedly admonished pharmacists that they could not cut off any doctor entirely. They could only evaluate each prescription on an individual basis. And they went further. An opioid compliance manager told an executive in an email, gathered during the inquiry and viewed by ProPublica, that Walmart’s focus should be on ‘driving sales.’”<sup>959</sup>

- xv. Similarly, a recent NPR investigation stated, “Walmart pharmacists warned for years about opioid sales that appeared dangerous or illegal” and that pharmacists faced “intense pressure to sell opioids and fill prescriptions quickly and without asking a lot of questions.”<sup>960</sup>
- xvi. In addition to the dispensing violations of the CSA summarized above, the DOJ Complaint alleges that, as the operator of its own distribution centers, which ceased distributing controlled substances in 2018, Walmart received hundreds of thousands of suspicious orders that it failed to report as required to by the DEA. The dispensing and distribution violations “helped to fuel the prescription opioid crisis.”<sup>961</sup> A DOJ press release further cited an example of a physician prosecuted

<sup>959</sup> Eisinger J., Bandler J. “Walmart Was Almost Charged Criminally Over Opioids. Trump Appointees Killed the Indictment.” ProPublica (March 25, 2020). Available at <https://www.propublica.org/article/walmart-was-almost-charged-criminally-over-opioids-trump-appointees-killed-the-indictment>.

<sup>960</sup> Mann, B., “Former Walmart Pharmacists Say Company Ignored Red Flags As Opioid Sales Boomed.” NPR (January 3, 2017). Available at <https://www.npr.org/2021/01/03/950870632/former-walmart-pharmacists-say-company-ignored-red-flags-as-opioid-sales-boomed>

<sup>961</sup> Press Release, *Department of Justice Files Nationwide Lawsuit Against Walmart Inc. for Controlled Substances Act Violations*, Department of Justice (December 22, 2020). Available at <https://www.justice.gov/opa/pr/department-justice-files-nationwide-lawsuit-against-walmart-inc-controlled-substances-act>

by the DOJ and convicted of illegal opioid distribution, who had specifically directed his patients to have their prescriptions filled at Walmart, adding that “Walmart’s own pharmacists reported concerns about the doctor up the corporate chain, but for years, Walmart did nothing—except continue to dispense thousands of opioid pills.”<sup>962</sup>

- xvii. Importantly, the DOJ Complaint states that “WALMART, AS A PHARMACY, VIOLATED THE CSA,”<sup>963</sup> rather than assigning blame to the individual pharmacists. I agree that the extent of CSA violations described in the DOJ Complaint cannot be attributed to individual pharmacists, but instead the responsibility must be attributed to the corporation itself. This is particularly true in light of the documented complaints from individual Walmart pharmacists to their supervisors asking for support in detecting and acting on red flags, which did not result in corporate support and hence unlawful dispensing continued.
- xviii. I am aware that Walmart filed a lawsuit against the DOJ and the DEA in October 2020, claiming that the company was constrained to fill doctors’ prescriptions, and that the DEA continued to allow those physicians to practice and prescribe.<sup>964</sup> I am also aware that a federal judge dismissed Walmart’s lawsuit, and that Walmart plans to appeal.<sup>965</sup>
- xix. In my opinion, Walmart, and other pharmacies, had an important role to play in preventing the distribution of opioids that fueled the epidemic, regardless of the actions of individual prescribers, government agencies, or the outcome of the litigation between Walmart and the DOJ. Walmart’s conduct, as described in the DOJ Complaint and news reports cited above, appears to be the result of careful investigation, and such conduct significantly contributed to the opioid epidemic.
- m. Pharmacy Defendant CVS failed to effectively control against diversion and undermined efforts of pharmacists to prevent diversion.

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<sup>962</sup> *Id.*

<sup>963</sup> Complaint in *United States of America v. Walmart Inc. and Wal-Mart Stores Easy, LP*, Case No: 1:99-mc-09999 (D. Del. 2020). Available at <https://www.justice.gov/opa/press-release/file/1347906/download>, at p. 29. (all caps in original.)

<sup>964</sup> Press Release, *Walmart Sues DOJ and DEA Seeking Clarity for Pharmacists in Dispensing Prescription Opioids*, Walmart (Oct. 22, 2020). Available at <https://corporate.walmart.com/newsroom/2020/10/22/walmart-sues-doj-and-dea-seeking-clarity-for-pharmacists-in-dispensing-prescription-opioids>

<sup>965</sup> Wilson, M., “Walmart to appeal dismissal of lawsuit against DOJ over opioids.” Chain Storage Age (Feb. 5, 2021). Available at <https://chainstoreage.com/walmart-appeal-dismissal-lawsuit-against-doj-over-opioids>.

- i. CVS was the target of DEA enforcement actions that provided explicit notice of the need to investigate and resolve red flags in order to dispense controlled substances.
- ii. One of the most commonly referenced DEA enforcement decisions that appears in the Pharmacy Defendants' own documents, as part of the rules for pharmacies to follow, is the *Holiday CVS* case, discussed above.<sup>966</sup> This case arose out of a lengthy DEA investigation and interaction between the DEA and CVS about dispensing opioids despite the red flags, in violation of the CSA. The mere fact that the case arose in Florida, rather than in Ohio or anywhere else in the country, has no bearing on CVS' responsibility to be aware of the red flags described in that case. Indeed, CVS' own Policies and Procedures say, "Employees are expected to fill and refill only legal and authorized prescriptions. They are expected to uphold this legal and moral responsibility by keeping up to date on all State and Federal changes in pharmaceutical jurisprudence."<sup>967</sup> The appearance of the *Holiday CVS* case in the NACDS summary of red flags, discussed above,<sup>968</sup> further confirms that all of the chain pharmacies, and especially CVS, were aware of the importance of that decision to their operations throughout the country. Because of the significance of that case, a brief review of its history is shown below.
- iii. In October 2010, Hillsborough, Florida, County Sheriff David Gee sent a letter to area CVS pharmacies, asking them "to work with law enforcement and closely scrutinize the prescriptions they receive in order to deal with the prescription drug epidemic in Florida."<sup>969</sup>
- iv. On December 8, 2010, the DEA hosted a meeting with representatives from CVS and the Florida Department of Health (DOH) where the DEA and DOH advised CVS that the diversion of oxycodone primarily involved fraudulent prescriptions, doctor shoppers, and unethical doctors.<sup>970</sup> At the meeting CVS was further advised of diversion "red flags" that a pharmacy should be familiar with including "(a) many customers receiving the same combination of prescriptions (i.e., oxycodone and alprazolam); (b) many customers receiving the same

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<sup>966</sup> See Section §C.6.j., above.

<sup>967</sup> CVS Pharmacy Operations Manual, Policy # 000-000-000, effective date 8/98; updated 9/04/03, 12/21/04; CVS-MDLT1-000055540, at 541. It was also well-known that prescriptions were filled in Florida were diverted and transported to Ohio and other states for sale, such that CVS' violations in Florida affected those other states. See, e.g., Beall, P. "How Florida spread oxy across America." The Palm Beach Post (July 6, 2018). <https://heroin.palmbeachpost.com/how-florida-spread-oxycodone-across-america/>

<sup>968</sup> See Section §C.6.j., above.

<sup>969</sup> MNK-T1\_0008415650 at 660.

<sup>970</sup> MNK-T1\_0008415650 at 658-569.

strength of controlled substances (i.e., 30 milligrams of oxycodone with 15 milligrams of oxycodone and 2 milligrams of alprazolam); (c) many customers paying cash for their prescriptions; (d) many customers with the same diagnosis codes written on their prescriptions (i.e., back pain, lower lumbar, neck pain, or knee pain); and (e) individuals driving long distances to visit physicians and/or to fill prescriptions.”<sup>971</sup> The DEA also informed CVS of a huge increase in oxycodone orders at one of its pharmacies and that in one 10 month period this pharmacy ordered 30 times more oxycodone than the typical pharmacy ordered in one year.<sup>972</sup> Additionally, the DEA informed CVS that “verifying that the prescription was written by a physician was not the same as making an independent determination that the prescription was written for a legitimate medical purpose in the usual course of professional practice.”<sup>973</sup>

- v. On August 12, 2011, DEA hosted a second meeting with representatives from Florida CVS pharmacies.<sup>974</sup> Once again, CVS was reminded of diversion red flags including the additional red flags of, “(f) customers coming into the pharmacy in groups, each with the same prescriptions issued by the same physician; and (g) customers with prescriptions for controlled substances written by physicians not associated with pain management (i.e., pediatricians, gynecologists, ophthalmologists, etc.)”<sup>975</sup>
- vi. On October 12, 2012, DEA Administrator Michele M. Leonhart’s August 2012 Final Order revoking the DEA registrations of two Florida CVS pharmacies was published.<sup>976</sup> The Final Order discusses several potential red flags including patients traveling long distances to the pharmacy, paying with cash, and using street names for controlled substances. The Order also discussed prescription cocktails like oxycodone and alprazolam, noting, that “even assuming that there are patients to whom a physician can legitimately prescribe these controlled substances simultaneously ... it is the totality of the red flags which renders them unresolvable and thus made the dispensings unlawful.”<sup>977</sup> Physician prescribing in a “factory like manner” with multiple patients

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<sup>971</sup> *Id.*, at 659.

<sup>972</sup> *Id.*, at 660-661.

<sup>973</sup> *Id.*, at 660.

<sup>974</sup> *Id.*, at 661.

<sup>975</sup> *Id.*, at 662.

<sup>976</sup> Press Release, DEA, *Holiday CVS Final Order Reveals Gross Negligence By Two CVS Pharmacies In Stanford, Florida* (Oct. 15, 2012), <https://www.dea.gov/press-releases/2012/10/15/holiday-cvs-final-order-reveals-gross-negligence-two-cvs-pharmacies>

<sup>977</sup> *Holiday CVS, L.L.C., v. Holder*, Civ. No. 1:12-cv-191 (D.D.C Fed. 24, 2012).

being described the same drug, in the same quantities, was also discussed as a red flag.<sup>978</sup>

- vii. *Holiday CVS* was the most expansive published DEA enforcement case against CVS, but it was not the only such decision. In April 2013, CVS agreed to pay \$11 million to settle civil penalty claims for record-keeping violation under the CSA.<sup>979</sup> From October 6, 2005 to October 5, 2011, CVS pharmacies in Oklahoma were alleged to have violated the CSA by “1) Creating, entering and maintaining invalid ‘dummy’ DEA registration numbers or numbers other than the valid DEA registration number of the prescribing practitioner on dispensing records, which were at times provided to state prescription drug monitoring programs; 2) Filling prescriptions for certain prescribers whose DEA registration numbers were not current or valid; and 3) Entering and maintaining CVS dispensing records, including prescription vial labels, in which the DEA registration numbers of non-prescribing practitioners were substituted for the DEA registration numbers of the prescribing practitioners.”<sup>980</sup> More recently, in April 2019, the DEA announced that CVS had agreed to pay \$535,000 to resolve allegations that several Rhode Island pharmacies “filled thirty-nine prescriptions for Percocet, a Schedule II narcotic, that CVS pharmacists had reason to know were forged.”<sup>981</sup>
- viii. Numerous CVS Policies and Procedures, summarized below, assigned responsibility to pharmacists to exercise sound professional judgment in reviewing potential indicators of forged or altered prescriptions, and other red flags, and instructed that only legitimate prescriptions for a proper medical purpose could be filled or refilled. While these Policies and Procedures were described as “mandatory,” in fact they were not. First, some of the so called “mandatory” policies gave pharmacists a list of discretionary steps (for example pharmacists “may” consult the PDMP); and second, the reality of time pressures, and understaffing, made it impossible to follow the procedures.<sup>982</sup>
- ix. An important action to detect potential illegitimate prescribing which CVS could have taken early on, but didn’t, was to require pharmacists

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<sup>978</sup> *Id.*

<sup>979</sup> Press Release, Dept. of Justice, CVS To Pay \$11 Million To Settle Civil Penalty Claims Involving Violations Of Controlled Substances Act, (Apr. 3, 2013) <https://www.justice.gov/usao-wdok/pr/cvs-pay-11-million-settle-civil-penalty-claims-involving-violations-controlled>.

<sup>980</sup> *Id.*

<sup>981</sup> Press Release, DEA, CVS to pay \$535,000 for filling invalid prescriptions, (Apr. 16, 2019), <https://www.dea.gov/press-releases/2019/04/16/cvs-pay-535000-filling-invalid-prescriptions>.

<sup>982</sup> Gabler, E. “How Chaos At Chain Pharmacies Is Putting Patients at Risk.” New York Times (January 31, 2020). <https://www.nytimes.com/2020/01/31/health/pharmacists-medication-errors.html>



to consult the applicable State PDMP (sometimes called “PMP,” or Prescription Monitoring Program) before dispensing a controlled substance, especially opioids. CVS did not *require* pharmacists to consult any other State PDMP, despite the purpose of those databases to provide the type of information pharmacists would need to determine whether a red flag could be resolved, which was essential to allow a flagged prescription to be dispensed.<sup>983</sup>

- x. No CVS Policy or Procedure that I have reviewed makes reference to pharmacists’ ability to utilize CVS’ own dispensing data to assist in identifying prescriber-related red flags such as overprescribing, prescribing of higher dosages, prescribing patterns, or percentage of controlled/non controlled prescribing, I infer from the absence of such reference that CVS did not make its database available to its pharmacists for such information. Not only did CVS fail to provide such data to assist pharmacists in making red flag decisions, but instead, CVS made such decisions more difficult by imposing the following rule in the “Corresponding Responsibility” paragraph of its 2004 Policy and Procedure on Professional Practices: “*Blanket decisions based on a practitioner’s prescribing habits or a customer’s appearance are unprofessional and may be illegal.* Each prescription must be analyzed individually to determine its merit and medical necessity.”<sup>984</sup> By requiring individualized review even in cases of pill mill-type prescribing, and by depriving pharmacists of CVS’ own data that would have identified such prescribers, CVS obstructed rather than implemented effective controls to prevent diversion.
- xi. The Professional Practices policy was renamed “Professional Standards,” and updated, in February 2012, shortly after CVS’ meetings with DEA over red flag concerns; at that time, the “Corresponding Responsibility” paragraph stated that this responsibility was “especially important with regard to prescriptions for controlled drugs.”<sup>985</sup> This provision referred the reader to the “Protocol for Dispensing Narcotic Drugs for Pain Treatment,” for further details as to exercise of the Corresponding Responsibility of pharmacists for controlled substance dispensing.<sup>986</sup>
- xii. CVS’ 2012 “Protocol for Dispensing Narcotic Drugs for Pain Treatment,”<sup>987</sup> ROPP-0061, stated that pharmacists must exercise their

<sup>983</sup> See, e.g., ROPP-0059, “Suspected Forged or Altered Prescriptions”, CVS-FLAG-000020192, at 20195, stating, “Compliance with this policy is mandatory,” yet at 20193-94, the same ROPP lists steps which “may” be taken to investigate, including “Consulting . . . (PMP), if available.”

<sup>984</sup> CVS Pharmacy Operations Manual, Policy # 000-000-000, effective date 8/98; updated 9/04/03, 12/21/04, CVS-MDLT1-000055540 at 543 (emphasis in original).

<sup>985</sup> CVS-MDLT1-000081508 at 512.

<sup>986</sup> *Ibid.*

<sup>987</sup> CVS-MDLT1-000081566.

professional judgment in deciding whether to fill a narcotic prescription, incorporating the Federal regulatory requirement that they have a “corresponding responsibility” to that of physicians to dispense medicines only for legitimate medical purposes. The ROPP provided a list of circumstances that give rise to suspicion or need for further investigation, such as practitioners who routinely prescribe the same medication in the same dosage to most or all of their patients, or who routinely prescribe the same combination of drugs for pain, “particularly where DEA has identified that combination as potentially abused,” (e.g. oxycodone, alprazolam, and Soma).<sup>988</sup> However, ROPP-0061 did not require, recommend or mention the use of the PDMP or CVS’ own database to answer such questions concerning practitioners’ habits.

- xiii. CVS’ ROPP-0061 is cross-referenced with ROPP-0062, “Prescription Drug Monitoring Websites,” adopted April 24, 2012.<sup>989</sup> This ROPP reiterates the “sound judgment” standard and states that a pharmacist “should” access a State’s PDMP “to augment your professional judgment when evaluating each controlled drug prescription, and should not be used as your sole determinant for filling/not filling a controlled substance.”<sup>990</sup> Again, accessing the PDMP was not required by ROPP-0062.
- xiv. ROPP-0062 was updated in May 2013. The revised version informed the pharmacists that the purpose of a PDMP was to assist in preventing diversion, “strongly encouraged” pharmacists to consult the PDMP “where appropriate in making an informed decision about whether or not to fill a prescription,” and provided examples of circumstances that might lead to the decision to use the PDMP, such as the type of drug being dispensed, whether there are “red flags present,” and whether PDMP information would assist in fulfilling the pharmacist’s “corresponding responsibility.”<sup>991</sup> Again, CVS declined to make it mandatory to consult the PDMP.
- xv. ROPP-0062 was revised multiple times after 2013; consulting the PDMP was never made mandatory.<sup>992</sup> The most recent available version of ROPP-0062 instructed pharmacists to follow state law as to when consulting the PDMP is mandatory, stating further, “In addition to following state laws, Pharmacists must also access and review PMP data whenever they identify red flags that are not able to be resolved or

<sup>988</sup> *Id.* at 566-67 (emphasis in original).

<sup>989</sup> CVS-MDLT1-000081545.

<sup>990</sup> *Id.* at 545-46.

<sup>991</sup> CVS-MDLT1-000081477 at 477-479.

<sup>992</sup> See, e.g., CVS-MDLT1-000081547 (July 2014); CVS-FLAG-000020985 (July 2015);

are reasonably certain that a person may be attempting to obtain a Schedule II-V controlled substance for a fraudulent, illegal, or a medically inappropriate purpose.”<sup>993</sup> As stated above, the PDMP itself is a primary source of information from which to identify red flags in the first place, and its value is diminished by making its use dependent on other, subjective factors that may or may not result in PDMP review by a particular pharmacist.

- xvi. CVS’ ROPP-0059 regarding “Suspected Forged or Altered Prescriptions,” stated that employees “must use common sense and exercise professional judgment” to decide whether a prescription was legitimate, and to only fill legitimate prescriptions.<sup>994</sup> Numerous factors were listed as examples of “[s]teps which *may* be used” to investigate legitimacy of a prescription, including “Consulting the state PMP, if available.” ROPP-0059 included a section entitled, “Minimizing the Likelihood of Diversion,” which provided that pharmacists “should” be familiar with diversion trends in their area and identify particular drugs and drug classes that presented higher risk of diversion, including oxycodone and hydrocodone, as well as benzodiazepines. However, while compliance with ROPP-0059 was “mandatory,” the various means of investigating red flags described in ROPP-5099 were *not* mandatory; instead, as in other CVS policies, the ROPP stated that a pharmacist “may” carry out investigations such as consulting the PDMP.<sup>995</sup>
- xvii. The 2012 version of CVS’ ROPP-0059, (“Last review date, December 17, 2013”) also included the “Minimizing the Likelihood of Diversion” section, which again identified particular drugs and drug classes that presented higher risk of diversion, and this version specified particular benzodiazepines (alprazolam and lorazepam) as presenting higher diversion risk. However, while compliance with ROPP-0059 was “mandatory,” the various means of investigating red flags described in ROPP-5099 were *not* mandatory; instead, the ROPP stated that a pharmacist “must” use common sense, but “may” carry out investigations such as consulting the PDMP.<sup>996</sup> Similar distinctions between mandatory use of common sense and non-mandatory use of the PDMP were carried forward in later versions of ROPP-0059.<sup>997</sup>

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<sup>993</sup> CVS-WASHAG-00000373 at 374.

<sup>994</sup> CVS-MDLT1-000081559 at 560.

<sup>995</sup> *Id.* at 565 (emphasis added).

<sup>996</sup> CVS-MDLT1-000081539 at 543.

<sup>997</sup> See, e.g., August 28, 2018 version, the most recent available for my review; CVS-WASHAG-00000294 at 295.

- xviii. In August 2014, CVS initiated the RxConnect Operational Prescriber Validation Policy and Procedures.<sup>998</sup> This provision outlined the system validations in place for prescriber information. Its purpose was to prevent prescriptions from being dispensed when prescriber did not have authority or had been blocked by CVS from being filled. The policy allowed CVS to block “prescribers who CVS, as part of corresponding responsibility, has decided not to dispense their controlled substance prescriptions.”<sup>999</sup> Contrary to the ROPP described above, effective in 2004, the 2014 policy appears to confirm that CVS had the ability to issue “blanket refusals to fill,” based on the prescriber’s behavior, regardless of patient red flags. Earlier adoption of such a policy could have blocked illegitimate opioid prescriptions from being dispensed, and also confirms that CVS’ own data enabled the company to make such determinations based on prescriber-related red flags, which could have been made accessible to pharmacists.
- xix. Also in 2014, CVS adopted ROPP 047561, Federal Guidelines for Controlled Substances. The provisions included rules for intake, storage and dispensing of controlled substances, including a list of Red Flags, divided into Patient Red Flags (Distance; Cash; Suspicious Behavior; Early Fills; Doctor Shopping; Appropriateness of Therapy) and Prescriber Red Flags (Professional Practice; Cocktails; Scope of Practice; Appropriateness of Therapy). The PDMP would have been informative as to these subjects, but CVS policy did not require consulting the PDMP unless required to do so by State law. Pharmacists were “strongly encouraged,” but not required, to consult the PDMP “for new prescriptions and for prescriptions for highly diverted drugs (e.g., Hydrocodone and Oxycodone).”<sup>1000</sup> Later versions required pharmacists to consult the PDMP whenever they “identify red flags that are not able to be resolved or are reasonably certain that a person may be attempting to obtain a Schedule II-V controlled substance for fraudulent, illegal or a medically inappropriate purpose,” or when required to do so by State law. Although acknowledging that such a review would provide a “more complete controlled substance use history to use their professional judgment” in deciding whether to fill the prescription or not, consulting the PDMP was not required.<sup>1001</sup>
- xx. In 2015, CVS adopted ROPP-049066: Controlled Substance Prescriber Monitoring and Review Program,<sup>1002</sup> which also related to prescribers’ whose behavior warranted consideration of blocking their opioid

<sup>998</sup> CVS-FLAG-000020264. This policy was updated without significant changes to the portion of the provision described above. E.g., CVS-FLAG-000020246 (2016); CVS-MDLT1B-000002289 (2019).

<sup>999</sup> *Id.*; CVS-FLAG-000020264.

<sup>1000</sup> CVS-FLAG-000020938 at 947-48.

<sup>1001</sup> CVS-FLAG-000020543 at 556 (2018); CVS\_WASHAG\_00000390 at 403 (2019).

<sup>1002</sup> CVS-FLAG-000020155. I have reviewed the September 2019 version, showing no significant changes. CVS-MDLT1B-000002258.

prescriptions. This program was designed to identify prescribers whose controlled substance prescriptions may be in violation of state and federal guidelines. The program aimed to further mitigate risk by resolving "red flag" prescribing trends associated with prescribers whenever possible. Elements of the program included creation of a Professional Practice team to conduct quarterly review of Tier 1 & Tier 2 Prescribers from a prescriber algorithm, as well as review and research of prescriber conduct from other sources, including state medical boards, news/media, and the DEA. Depending on the findings of the review, prescribers could be suspended from filling prescriptions at CVS stores.<sup>1003</sup> Such a program, including use of CVS' own data to create a prescriber algorithm, could have been implemented 15 years earlier, when the opioid epidemic was known, but less harm had been done. To the extent that the Controlled Substance Prescriber Monitoring and Review Program was successfully implemented in and after 2015, its earlier use would have prevented diversion and the risks of addiction, overdose, and mortality in prior years.

- xxi. In July 2018, CVS revised ROPP-0061, stating: "CVS Pharmacy pharmacists are required to document all steps taken to resolve red flags associated with controlled substance prescriptions in the patient profile. The documentation must clearly justify the determination and appropriateness of the therapy dispensed. Documentation *may* include, but it is not limited to: diagnosis, PMP check, Prescriber conversation, treatment or taper plan. Any prescriber office conversation notations must also include the person spoken to, the date and the time."<sup>1004</sup> Consistent with past versions of the policy, and with the statement that documentation "may" include PMP check, the revised ROPP-0061 did not require checking the PDMP unless State law required it, or "when in the professional judgment of the Pharmacist such data would assist in making a corresponding responsibility determination."<sup>1005</sup>
- xxii. The emphasis on speed and sales at the expense of patient safety was exacerbated by CVS' incentive programs. For example, the CVS "2006 Pharmacist Incentive Plan" stated the objective, "to motivate employees to exceed top line results and maximize store profits, while maintaining high levels of customer service. . . . Incentive awards are based on actual results measured against re-established financial goals and individual performance objectives."<sup>1006</sup> An "Incentive Opportunity" provided additional monetary compensation based on each store's

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<sup>1003</sup> CVS-FLAG-000020155 at 155-158.

<sup>1004</sup> CVS-WASHAG-00000359 at 361 (emphasis added).

<sup>1005</sup> *Id.* at 360.

<sup>1006</sup> CVS-MDLT1-000060949-950.

average weekly script volume, and “Rx Executables” measured the “Pharmacist’s performance against operational activities that drive pharmacy sales and store profit.”<sup>1007</sup> The Incentive Plan made no mention of pharmacy goals to avoid medication errors or enhance patient safety. Financial incentive plans based on profits and prescription sales inevitably conflict with the need for careful, diligent and inherently time-consuming investigation of red flags for dispensing of controlled substances, and the DEA ultimately cited such programs as contributors to the prescription opioid epidemic.<sup>1008</sup> I agree that these programs contributed to the epidemic and hindered, rather than helped, in the requirement of effective controls against diversion.

- xxiii. In the absence of mandatory review of the Ohio PDMP (OARRS) and considering the typical time constraints to which pharmacists are subjected, not to mention that Ohio was experiencing an epidemic of prescription opioid misuse and mortality, it is highly likely that substantial numbers of prescriptions were misused and/or diverted and further contributed to the epidemic.
- n. Defendant Rite Aid failed to effectively control against diversion and undermined the efforts of Pharmacists to prevent diversion.
  - i. Rite Aid’s role in the opioid epidemic parallels those of Walmart, CVS and Walgreens, as described above. Policies ostensibly designed to control diversion were undermined by incentivized prescribing, understaffing, and poor enforcement, resulting in dispensing of controlled substances in violation of the CSA, and enforcement actions taken by the DEA.
  - ii. In 2009, Rite Aid paid \$5 million to resolve DEA claims of violations of the CSA. “Rite Aid knowingly filled prescriptions for controlled substances that were not issued for a legitimate medical purpose pursuant to a valid physician-patient relationship.... Additionally, the DEA conducted accountability audits of controlled substances at 25 of the 53 stores investigated to determine whether Rite Aid could properly account for Schedule II and III controlled substances purchased and dispensed. *The results of the accountability audits revealed significant shortages or surpluses of the most highly abused drugs, including oxycodone and hydrocodone products, reflecting a pattern of non-compliance with the requirements of the CSA and federal regulations*

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<sup>1007</sup> *Id.* at 951.

<sup>1008</sup> WAGMDL00709398.



*that lead to the diversion of controlled substances in and around the communities of the Rite Aid pharmacies investigated.”<sup>1009</sup>*

- iii. Rite Aid incentivized its pharmacists to fill more prescriptions, including opioid prescriptions. In 2006-2008, Rite Aid’s staff pharmacists were eligible for a Store Bonus Program based on 80% from store profits and 20% from customer satisfaction; profits from controlled substance prescriptions were included in the bonus calculations.<sup>1010</sup> This structure created a conflict of interest for pharmacists by having their compensation depend on filling as many prescriptions as possible. Also, to the extent that the bonus was dependent on customer satisfaction, that metric would suffer if prescriptions for controlled substances were not filled.
- iv. According to Rite Aid’s 2009 Store Bonus Program, “script achievement” was “one of two criteria used to determine and calculate bonus awards for all eligible Pharmacy participants.”<sup>1011</sup> Bonuses were based on 50% for prescription achievement and 50% for customer satisfaction.<sup>1012</sup> The prescription achievement metric was calculated “by dividing the store’s actual Script performance by the plan figure.”<sup>1013</sup> Also in 2009, Rite Aid structured the pharmacist incentive policy in its “Prescription Incentive Bonus Program,” which was “designed to reward our pharmacy & front end associates for increasing their overall prescription business.”<sup>1014</sup> That policy encouraged pharmacists to contact patients to pick up orders for “pain medicine” to increase prescription sales.<sup>1015</sup> Rite Aid’s 2009 bonus incentive policy continued through multiple iterations.<sup>1016</sup>
- v. Rite Aid’s documents show awareness by 2009 that “Oxycontin and hydrocodone have become two of the most abused prescription medications in the United States. The DEA considers the pharmacist as the ‘gate keeper’ of these controlled substances.”<sup>1017</sup> Despite this

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<sup>1009</sup> Press release, “Rite Aid Corporation and Subsidiaries Agree to Pay \$5 Million in Civil Penalties to Resolve Violations in Eight States of the Controlled Substances Act.” Department of Justice (January 12, 2009). <https://www.justice.gov/opa/pr/rite-aid-corporation-and-subsidiaries-agree-pay-5-million-civil-penalties-resolve-violations> (emphasis added).

<sup>1010</sup> See Rite\_Aid\_OMDL\_0060638, Rite\_Aid\_OMDL\_0060671, Rite\_Aid\_OMDL\_0060684

<sup>1011</sup> See Rite\_Aid\_OMDL\_0060717, at 0060719; *see also* Scott Jacobson, 103:20-104:5.

<sup>1012</sup> See Rite\_Aid\_OMDL\_0060717, at 0060719.

<sup>1013</sup> *Id.*

<sup>1014</sup> Rite\_Aid\_OMDL\_0055395, at 0055397.

<sup>1015</sup> *Id.*, at 0055396.

<sup>1016</sup> See Rite\_Aid\_OMDL\_0060767; Rite\_Aid\_OMDL\_0060855; Rite\_Aid\_OMDL\_0060872; Rite\_Aid\_OMDL\_0060894.

<sup>1017</sup> Rite\_Aid\_OMDL\_0046560-561; email from Janet Hart, Rite Aid’s Director of Government Affairs, to Scott Jacobson, Rite Aid’s Vice President of Pharmacy Operations, and DEA Memo attachment.

awareness, Rite Aid expressed the view that the sale of controlled substances could increase business. In an internal 2010 Rite Aid email, Rite Aid corporate employees discussed opportunities to grow Schedule II prescriptions. The email states, “we would then target stores that fell below the average and have discussions...surrounding *future CII opportunities*.”<sup>1018</sup> The sale of addictive and dangerous drugs should not have been seen as an “opportunity,” and that view is emblematic of the approach that gave rise to, and has prolonged, the opioid epidemic.

- vi. Rite Aid’s rules regarding the “corresponding responsibility” to assure legitimate prescriptions during this same time period were minimal, even by comparison to the inadequate standards of the other chain pharmacies. In 2010, Rite Aid’s policies and procedures for dispensing controlled substances consisted of a 2010 “DEA Reminder Message,” which stated the need for a “valid prescriber/patient relationship,” a responsibility to “verify the valid relationship” and that a pharmacist “should exercise professional judgment when dispensing” prescriptions generated from the Internet.<sup>1019</sup> This bare bones advice offered no guidance as to how to fulfill the stated responsibilities. Further, in light of the pressure to prescribe quickly, Rite Aid’s pharmacists would have had no time to properly verify that the prescription met the CSA threshold for a legitimate medical condition within the usual scope of practice. Rite Aid acknowledged in a 2010 PowerPoint presentation, in a review of “What We Have in Place,” that Rite Aid only “developed the minimum compliance standards in 12 of the higher risk regulatory and operational compliance areas.”<sup>1020</sup>
- vii. In 2011, Rite Aid’s “2011 Game Plan” memo<sup>1021</sup> stated, “We must fill more prescriptions, our future as a company is dependent on this fact...Staffing our stores with the right Pharmacist and Technicians dedicated to growing the business and being the best Health Care Provider is non-negotiable.”<sup>1022</sup> This formulation of the “Game Plan” failed to take into account that the drive to “fill more prescriptions,” and the financial incentives to pharmacists to do so, were antithetical to the other stated goal of being the “best Health Care Provider,” as shown in the numerous studies reporting that pharmacist error rates increase in proportion to the speed with which prescriptions are filled.<sup>1023</sup> A more appropriate “Game Plan” would have included requiring pharmacists to

<sup>1018</sup> See Rite\_Aid\_OMDL\_0143733 (emphasis added).

<sup>1019</sup> Rite\_Aid\_OMDL\_0044272, at 0044273.

<sup>1020</sup> Rite\_Aid\_OMDL\_0049319, at 0049340.

<sup>1021</sup> See Rite\_Aid\_OMDL\_0132710.

<sup>1022</sup> *Id.*; see also Scott Jacobson, 80:19-81:14.

<sup>1023</sup> See, e.g., discussion of New York Times, Chicago Tribune and University of Arizona investigations, at Section §C.6.i of this report.

investigate “red flags”, for example by consulting the PDMP, before dispensing opioids. Their burden of responsibility was heightened given that the nation is in the midst of an opioid epidemic, which was peaking when Rite Aid’s “Game Plan” was formulated.

- viii. Consistent with its Game Plan, a 2011 internal Rite Aid presentation described the role of Rite Aid’s Pharmacy District Managers: “Driving Top-line prescription sales through aggressive prescription growth – This is YOUR NUMBER 1 JOB!”<sup>1024</sup> The presentation further stated, “You and your pharmacy manager are accountable for prescription count exceeding plan,”<sup>1025</sup> and stated the Pharmacy District Manager responsibilities were to “maximize profits” and “work with a Sense of Urgency to drive financial performance”<sup>1026</sup>
- ix. The same 2011 internal presentation addressed Rite Aid’s “15 Minute Prescription Guarantee,”<sup>1027</sup> stating, “we introduced the ‘Ready in 15 Minutes’ service goal over 7 years ago...”<sup>1028</sup>, and “our competition cannot match this level of service.”<sup>1029</sup> In reality, Rite Aid’s pharmacists typically spent far less than 15 minutes on each prescription. In fact, according to a University of Cincinnati study of Rite Aid’s prescription fill rates in 2011,<sup>1030</sup> Rite Aid pharmacists spent an average of 3.22 minutes on any given prescription, or 18.66 scripts per hour.<sup>1031</sup> This fill rate is a recipe for prescribing errors, providing inadequate time to investigate red flags or fulfill the corresponding responsibility to dispense controlled substances only for legitimate medical purposes.
- x. In 2012, Rite Aid’s controlled substance policy added a “Weekly Pharmacy Communication” that included a section entitled, “How to Identify if a Prescription is Valid,”<sup>1032</sup> listing seven circumstances “that might warrant a ‘second look’ and further follow-up.”<sup>1033</sup> However, like the other Pharmacy Defendants, Rite Aid did not require their pharmacists to use the Ohio OARRS/PDMP for “further follow-up.” A

<sup>1024</sup> Rite\_Aid\_OMDL\_0137944, at 137949; (emphasis in original).

<sup>1025</sup> *Id.*; see also Deposition of Scott Jacobson, March 10, 2021, *In Re: National Prescription Opiate Litigation*, 89:2-9.

<sup>1026</sup> Rite\_Aid\_OMDL\_0137944, at 137951; (emphasis in original).

<sup>1027</sup> See Rite\_Aid\_OMDL\_0137944, at 138077.

<sup>1028</sup> *Id.*, at 138148.

<sup>1029</sup> *Id.*, at 138082.

<sup>1030</sup> See Rite\_Aid\_OMDL\_0128107; see also Deposition of Scott Jacobson, March 10, 2021, *In Re: National Prescription Opiate Litigation*, 95:21-96:6.

<sup>1031</sup> See Rite\_Aid\_OMDL\_0128107, at 0128116; see also Deposition of Scott Jacobson, March 10, 2021, *In Re: National Prescription Opiate Litigation*, 99:14-100:9.

<sup>1032</sup> See Rite\_Aid\_OMDL\_0056851, at 0056855-56.

<sup>1033</sup> *Id.*, at 56856.

Rite Aid policy adopted as of 10/24/2011 stated that “prior to dispensing a prescription for a controlled substance a pharmacist *should* request an OARRS report” if certain criteria are met.”<sup>1034</sup> Similarly, Rite Aid’s 2014 OARRS policy listed certain situations in which “the pharmacist must query OARRS,”<sup>1035</sup> but those situations would not have been apparent to the pharmacist responsible for making the decision to consult OARRS or not, if the purchaser sought to avoid detection, for example, by shopping at different chain pharmacies. As late as 2019, Rite Aid pharmacists’ failures to use OARRS were described by Mark Obert, Rite Aid’s then-District Manager, as “recurring issues that we need to address,” after multiple Board of Pharmacy inspections at Rite Aid pharmacies revealed deficiencies.<sup>1036</sup>

- xi. As with the other Pharmacy Defendants, no Rite-Aid policies called for the company to provide its pharmacists with analyses from their own data sets concerning controlled substance prescriptions or the doctors who prescribed them. This data was available to Rite Aid and should have been provided to the pharmacists, to help them to identify red flags of frequent, high volume, cocktail, or high dose prescribers.
- xii. On March 1, 2013, Rite Aid adopted a corporate monitoring program called the High Alert Review Process.<sup>1037</sup> The program listed “prescriber” red flags, including pattern prescribing, large quantities prescribed, and distance traveled; pharmacists were told “in order for a prescription to be valid, there must be a proper patient-prescriber relationship,” and that red flags “MAY indicate that a proper patient-prescriber relationship does not exist.”<sup>1038</sup> However, Rite Aid did not provide pharmacists with analysis of its own data to determine the presence or absence of prescriber red flags. Further, the policy directed pharmacists to consult the PDMP “*if* the prescription or patient is suspicious,”<sup>1039</sup> depriving pharmacists of the most appropriate tool to make that determination in the first place.
- xiii. During the same time period, in 2013, Rite Aid continued to undermine the goal of preventing controlled substance diversion by instituting new financial incentives for increased prescriptions. Rite Aid’s “Pay for Performance (P4P)” model adjusted compensation based on whether

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<sup>1034</sup> Rite\_Aid\_OMDL\_0033915 (emphasis added).

<sup>1035</sup> Rite\_Aid\_OMDL\_0077968; e.g., Patient receiving OARRS drugs from multiple prescribers or for more than 12 weeks. These facts could avoid detection through use of multiple pharmacies.

<sup>1036</sup> See Rite\_Aid\_OMDL\_0088975, at 0088977

<sup>1037</sup> See Rite\_Aid\_OMDL\_0044327 (noting Oxycodone 30mg and Hydrocodone 10/325 are among the drugs Rite Aid “will continue to monitor”).

<sup>1038</sup> Rite\_Aid\_OMDL\_0044379, at 44381 (emphasis in original).

<sup>1039</sup> *Id.*, at 44383.

the pharmacy met certain business goals, such as increasing prescription counts.<sup>1040</sup> Specifically, the P4P program stated, “Overall Compensation Performance Summary will reflect an increase in compensation as a result of increasing store designation through increased prescription counts.”<sup>1041</sup> A 2013 internal Rite Aid memo stated, “Simply, P4P will additionally recognize Rite Aid’s pharmacists in higher prescription volume pharmacies with higher compensation and target bonus incentive.”<sup>1042</sup>

- xiv. In 2015, Rite Aid ultimately excluded controlled substances from prescription counts for its pharmacist bonus calculations.<sup>1043</sup> Nevertheless, the “Customer Service” bonus component continued to provide an incentive to fill illegitimate prescriptions, since “Customer Service” ratings would fall based on complaints for a pharmacist’s refusal to fill a suspicious prescription, thereby negatively impacting that pharmacist’s bonus.<sup>1044</sup> Rite Aid continued this policy structure through at least fiscal year 2019.<sup>1045</sup> Rite Aid accordingly continued to financially incentivize its pharmacists to fill as many prescriptions as possible, even if a pharmacist suspected a prescription is likely subject to diversion.
- xv. In 2015, Rite Aid implemented the “NexGen Automated Red Flag Documentation Process for High Alert Controlled Substances.” The process and steps for the pharmacist to take were similar to the 2013 procedure, except that NexGen is a computer system where pharmacists could document their due diligence in validating the legitimacy of High Alert controlled substances prescriptions. Red flag validation questions were listed on the system, and “responses to these questions will also assist in Step 5, the use of your professional judgment to determine whether or not to dispense.” Unlike the 2013 process, a response of “no” to “validate prescription” or “validate prescriber” “will result in an auto fail of the Red Flag Process. Once the Pharmacist acknowledges the rejection of the prescription, it will auto delete and will not be able to be reactivated” (but will remain on the patient’s profile). If the process is rejected, the “QA reviewing Pharmacist must select a reason from the drop down menu and biometrically acknowledge the rejection [and] the rejected prescription will be automatically deleted” (but the information will be saved and displayed with a Red Flag icon in the patient’s medication history, which must be reviewed to perform the

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<sup>1040</sup> See Rite\_Aid\_OMDL\_0082409.

<sup>1041</sup> *Id.*, at 0082409.

<sup>1042</sup> Rite\_Aid\_OMDL\_0082405.

<sup>1043</sup> See Rite\_Aid\_OMDL\_0035161, at 0035164.

<sup>1044</sup> *Id.*, at 0035164.

<sup>1045</sup> See Rite\_Aid\_OMDL\_0035282; Rite\_Aid\_ONY\_000001; Rite\_Aid\_ONY\_000247; Rite\_Aid\_ONY\_000230.

required DUR). Significantly, the 2015 procedure was identical to the 2013 procedure as to the critical issue of consulting the PDMP; in particular, the procedure stated that the pharmacist “should” review the PDMP “*if* the prescription or patient is suspicious,”<sup>1046</sup> rather than requiring that the pharmacist take the protective step of consulting the PDMP for all controlled substance prescriptions.

- xvi. In March 2017, Rite Aid paid \$834,200 in civil penalties to settle claims stemming from violations of the CSA. A DEA “investigation revealed the incorrect or invalid registration numbers were used at least 1,298 times as a result of Rite Aid’s failure to adequately maintain its internal database,” and Rite Aid pharmacies also “dispensed, on at least 63 occasions, prescriptions for controlled substances written by a practitioner whose DEA registration number had been revoked by the DEA for cause.” These penalties, while not the largest paid by Rite Aid or other Pharmacy Defendants, nevertheless show that Rite Aid has continued to violate the CSA by improperly dispensing controlled substances in the relatively recent past, despite having been previously penalized.
- xvii. Rite Aid recently acknowledged that financial incentives specifically to sell prescription opioids were inappropriate. The 2019 Board Report on Opioid Oversight states, “Rite Aid has taken effective measures to ensure that all of its pharmacy personnel responsible for filling prescriptions for controlled substances are not financially incentivized or otherwise encouraged to fill such prescriptions.”<sup>1047</sup> Unfortunately, such belated measures could never undo the harm of two decades of over-dispensing. Pharmacists should never have been incentivized to sell more addictive, potentially fatal drugs in the first place, especially since the ravages of the prescription opioid epidemic were well known by the time Rite Aid implemented such programs.
- xviii. Recently on June 4, 2019, Federal and state investigators executed search warrants at five Rite Aid pharmacies in northeast Ohio. The DEA indicated that the investigation was related to suspected “irregularities in dispensing practices.” In its public statement about the raids, DEA pointed to the laws imposing an independent duty of a

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<sup>1046</sup> Rite\_Aid\_OMDL\_0044351, at 355 (emphasis added).

<sup>1047</sup> Rite Aid Board Report on Opioid Oversight, at 6. <https://www.riteaid.com/content/dam/riteaid-web/corporate/Rite%20Aid%20Board%20Report%20on%20Opioids%20Oversight.pdf>



pharmacist to verify and ensure that prescriptions are issued for a legitimate medical purpose.<sup>1048</sup>

- o. Defendant Kroger failed to effectively control against diversion and undermined the efforts of Pharmacists to prevent diversion.
  - i. In 2005, Kroger entered into a settlement with DEA regarding its compliance programs concerning controlled substances.<sup>1049</sup> The settlement involved Kroger's handling of controlled substances in its stores in Colorado, Wyoming, New Mexico and Utah, after an audit revealed "serious record-keeping and controlled substances security problems" such that "it was not possible to determine how many drugs had been lost or diverted or who was responsible for potential diversion."<sup>1050</sup> Kroger paid \$7 million in settlement and agreed to "implement a Comprehensive Regulatory Compliance Program," and to train all of its employees pursuant to the Compliance Program.<sup>1051</sup>
  - ii. Subsequent to the 2005 DEA settlement, Kroger developed standard operating procedures (SOPs) for its pharmacies that included a list of "criteria [that] may indicate that the purported prescription was not issued for a legitimate medical purpose."<sup>1052</sup> In other words, red flag criteria. Six criteria were listed, but did not include several well-known red flags, including individuals paying in cash and individuals who appear to be under the influence of drugs.<sup>1053</sup> Kroger knew, or should have known, that there were additional red flags that pharmacists should be considering. (see section §C.6.i.of this report).
  - iii. In November 2012, Kroger learned of DEA license revocation actions against a Cardinal Health distribution center, a Walgreens distribution center, and seven retail pharmacies, two of which were CVS stores and three of which were Walgreens stores.<sup>1054</sup> Kroger retained Buzzeo

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<sup>1048</sup> Nethers, D. Federal agents execute search warrants at several Rite Aid pharmacies, FOX 8 CLEVELAND (June 4, 2019, 4:22 PM), <https://fox8.com/2019/06/04/federal-agents-execute-search-warrants-at-several-rite-aid-pharmacies>.

<sup>1049</sup> Kroger-MDL00031079.

<sup>1050</sup> Kroger-MDL00031079.

<sup>1051</sup> Kroger-MDL00031079 at -1082.

<sup>1052</sup> KrogerSmithNMAG00003033 at -3091.

<sup>1053</sup> For a more complete list of red flags, see §C.6.i.vii, above.

<sup>1054</sup> KrogerSmithNMAG00010074; KrogerSmithNMAG00010231.

PDMA Consultants (“Buzzeo”)<sup>1055</sup> to perform a compliance audit.<sup>1056</sup> As part of that audit, Buzzeo visited two Kroger pharmacies and interviewed pharmacists.<sup>1057</sup> In its report dated March 12, 2013, Buzzeo found that “Kroger line Pharmacists were not familiar with the term ‘suspicious order monitoring’ and did not remember receiving any information from Kroger’s corporate offices regarding prescription ‘red flags.’ Pharmacists appeared to know in general about their practice responsibilities but were not fully familiar with the term and meaning of ‘corresponding responsibility.’”<sup>1058</sup> The report stated, “Indeed, the distribution center SOPs in some cases provide improper guidance on DEA regulations and need revision and improvement from a DEA standpoint.”<sup>1059</sup> Also, “It further appeared from interviews with line pharmacists that there is some level of acceptance regarding patients who are being treated by pain management clinics who may be receiving large amounts of controlled substances. Staff clearly cooperates with law enforcement and regulatory authorities; however, there was no evidence of discussing drug abuse trends with any agency or person, as envisioned by Kroger’s Pharmacy SOPs. As noted above, Kroger’s corporate effort to provide training on patient and/or physician abuse practices (red flags) was not successful based on the interviews conducted at the two pharmacies.”<sup>1060</sup> The report emphasized a failure of leadership at the corporate level.

- iv. Near the end of 2012, Kroger instructed pharmacies to remove incentives in the bonus program for controlled substance prescriptions.<sup>1061</sup> This policy change came only after DEA took disciplinary action against other chain pharmacies due to excessive oxycodone dispensing.<sup>1062</sup> Prior to 2012, Kroger’s Store Level Bonus Plan provided that pharmacists’ bonuses would be based on individual pharmacy results, and higher prescription counts would result in higher bonuses, and lower prescription counts would lead to smaller bonuses.<sup>1063</sup> Pharmacists thus had an incentive to ignore red flags, as

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<sup>1055</sup> Ronald Buzzeo, R.Ph., is a former Deputy Director of the Office of Diversion of the DEA.

KrogerSmithNMAG00003033 at 3035. He practiced as a pharmacist prior to beginning his law enforcement career as a Narcotic Investigator with the New York State Department of Health, Bureau of Narcotic Control. *Id.* After several years, he entered federal service with the Bureau of Narcotics and Dangerous Drugs, the predecessor agency to the DEA, where he served for 22 years until his retirement from federal service in 1990. *Id.*

<sup>1056</sup> KrogerSmithNMAG00013075; KrogerSmithNMAG00013077.

<sup>1057</sup> KrogerSmithNMAG00013077 at -3079.

<sup>1058</sup> KrogerSmithNMAG00013077 at -3079.

<sup>1059</sup> KrogerSmithNMAG00013077, at -3085, footnote 11.

<sup>1060</sup> KrogerSmithNMAG00013077, at -3085.

<sup>1061</sup> KrogerSmithNMAG00010074 at 00010075.

<sup>1062</sup> KrogerSmithNMAG00010074.

<sup>1063</sup> Deposition of Jamie McDermott, February 22, 2022, *State of New Mexico, ex rel. vs. Purdue L.P., et al.* D:101-cv-2017-02541, at 38:3-41:22.

any controlled substance prescription they investigated would take time away from filling, which, together with any prescription they ultimately refused to fill, would lower their prescription count and negatively impact their bonus.

- v. In 2014, nearly ten years after the settlement with the DEA, Kroger's Compliance Manager, Jeffrey Loesch, conducted ongoing assessments of Kroger's level of regulatory compliance and evaluated and ranked areas of most significant risk with respect to DEA compliance. Loesch was responsible for Kroger's pharmacy compliance program across its 2,200-plus pharmacies.<sup>1064</sup> The number one risk he identified was Kroger's "pharmacists' inconsistent and often absent understanding of the DEA's expectations for executing proper corresponding responsibility related to the dispensing of controlled substances."<sup>1065</sup> When asked whether a pharmacist presented with red flags was required to resolve them, Mr. Loesch replied: "It would be my responsibility and practice to make sure that I felt comfortable with the dispensing of the prescription. That may or may not include resolving all red flags."<sup>1066</sup> Yet resolving red flags is an inherent part of a pharmacists' corresponding responsibility. Further, in a July 2015 presentation by Jeffrey Loesch on controlled substance compliance, in a slide titled "What Must Pharmacists Do", the first bullet point states, "If Red Flags are present, the pharmacist must be able to resolve them."<sup>1067</sup>
- vi. Kroger's version 5.2 of its Policies and Procedures—released in 2016—still continued to list only the same six red flags to indicate prescriptions not issued for a legitimate medical purpose as the 2005 version.<sup>1068</sup>
- vii. In discovery, Kroger provided its records of the opioid prescriptions it dispensed to Cobb County residents during the period November 2008 through June 2018. During that period, Kroger dispensed 598,854 opioid prescriptions, representing, 28,310,705 dosage units, to Cobb County residents. According to Plaintiffs expert Carmen Catizone's red flag analysis, of those 598,854 dispensed prescriptions, 278,910 prescriptions triggered at least one red flag; 136,699 triggered at least

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<sup>1064</sup> Deposition of Jeffrey Loesch, July 7, 2022, *Montgomery County v. Cardinal Health, Inc., et al.* Case No. 1:18-op46326-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 7) (herein after "Loesch Dep."), at 30:7-31:5.

<sup>1065</sup> KrogerMDL00034861 at -4865; See also: Loesch Dep. at 284:22285:20. Loesch could not recall what, if anything, was done to address that risk. Loesch Dep. at 296:6-296:18.

<sup>1066</sup> Loesch Dep. at 81:01-81:21, 97:12-99:19.

<sup>1067</sup> KrogerMDL00006337, at -6374.

<sup>1068</sup> KrogerMDL00000302, KrogerMDL00000329, at -0399.

two red flags; 58,437 triggered at least three red flags; and 24,711 triggered at least four red flags.<sup>1069</sup>

- p. Defendant Publix failed to effectively control against diversion and undermined the efforts of Pharmacists to prevent diversion.
  - i. Publix recognized the importance of regulations around controls for controlled substance prescriptions but characterized these safeguards as a “burden” for the retailer and distributor.<sup>1070</sup>
  - ii. Publix has dispensed controlled substances since 1986, but Publix did not create a written controlled substance dispensing policy that referred to red flags of diversion until it learned of an intermediate suspension order issued against CVS in 2012 (and later Walgreens).<sup>1071</sup>
  - iii. In 2012, Publix issued a guide referencing the identification of red flags in Ch. 8 of the “Pharmacy Reference Procedure Guide” titled “Regulations and Associated Publix Policies,”<sup>1072</sup> but interns, pharmacists, and managers were not provided with formal training on this guidance.<sup>1073</sup> Publix justified its failure to provide such training on the basis that “pharmacy associates should know the requirements for a controlled substance prescription.”<sup>1074</sup>
  - iv. Shannon Brice, who was a pharmacist at Publix for 25 years and also served as a pharmacy manager responsible for other pharmacists in Cobb County, testified that she first saw the 2012 guide while preparing for her deposition in this litigation,<sup>1075</sup> suggesting that the 2012 written policy was not incorporated into pharmacists’ training or education.
  - v. Publix’s dispensing policy did not require documentation of red flag except on a state-by-state basis, which did not include Georgia.<sup>1076</sup> Publix dispensing policy did not require checking of the PDMP,<sup>1077</sup>

<sup>1069</sup> Plaintiff’s CT8 Amended and Superseding Red Flag Analysis served September 19, 2023, pursuant to Section D.2 of CMO.

<sup>1070</sup> PUBLIX-MDLT8-00071828.

<sup>1071</sup> PUBLIX-MDLT8-00027405. Publix opened its first pharmacy in Cobb County in 1992. PUBLIX-MDLT8-00132845 at -2847; PUBLIX-MDLT8-00115539-PUBLIX-MDLT8-00115540.

<sup>1072</sup> PUBLIX-MDLT8-00002439 at 00002475.

<sup>1073</sup> Deposition of Rodney Michael King, November 30, 2022, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8) (hereinafter “King Dep.”), at 133:2-22-135:17.

<sup>1074</sup> PUBLIX-MDLT8-00002439 at 00002474.

<sup>1075</sup> Deposition of Shannon L. Brice, August 3, 2023, *Cobb County v. Purdue Pharma, et al.*, Case No. 1-18-op-45817-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), (hereinafter “Brice Dep.”), at 42:21-45:8.

<sup>1076</sup> PUBLIX-MDLT8-00027405 at 27443.

<sup>1077</sup> *Id.*

unless required by the state, and Georgia law does not require pharmacists to consult the PDMP before dispensing a controlled substance.<sup>1078</sup>

- vi. Publix did not hire diversion analysts until 2018.<sup>1079</sup> In November of 2018, Publix approved its first controlled substance training course.<sup>1080</sup> At that time, Publix was still developing a comprehensive training program for pharmacy staff to identify red flag prescriptions.<sup>1081</sup> Controlled substance training on red flags and patient care was considered a high effort and low priority for Publix.<sup>1082</sup> In sum, Publix had no formal or rigorous controlled substance compliance training prior to 2019.<sup>1083</sup>
- vii. No one at Publix was responsible for auditing its dispensing practices. Rodney King (Atlanta Division Pharmacy Operations Manager, 2004-2017)<sup>1084</sup> could not recall doing anything with respect to reviewing compliance of controlled substances, other than conducting physical visits to the stores or seeing reports that would show stores that were “edging up to their upper limit,” of which he would notify the store supervisor.<sup>1085</sup>
- viii. Publix does not require its pharmacists to document due diligence related to clearing red flag prescriptions.<sup>1086</sup> Kathy Leonard (Publix’s Director of Retail Pharmacy Operations, 2020 to present)<sup>1087</sup> minimized the importance of documenting due diligence: “How things are documented and in what way can be equally as damaging.... So

<sup>1078</sup> See Georgia Department of Public Health. Prescription Drug Monitoring Program Report, Georgia, 2018, at p. 3 (beginning July 1, 2018, prescribers were required to check the PDMP before prescribing controlled substances, but there is no requirement that pharmacists do so before dispensing).

<sup>1079</sup> Deposition of Chris Hewell, November 4, 2022, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. In *Re: National Prescription Opiate Litigation* (MDL 2804, Track 8), at 149:24-150:2.

<sup>1080</sup> PUBLIX-MDLT8-00072578 (P-PUB-0319); Deposition of Jillanne Smith, November 15, 2022, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. In *Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), at 403:18-25.

<sup>1081</sup> PUBLIX-MDLT8-00079714 at 79716.

<sup>1082</sup> PUBLIX-MDLT8-00119095.

<sup>1083</sup> PUBLIX-MDLT8-00119095. See also PUBLIX-MDLT8-00079714; PUBLIX-MDLT8-00088571; PUBLIX-MDLT8-00134424.

<sup>1084</sup> King Dep. at 72:4-73:4.

<sup>1085</sup> King Dep. at 231:1-232:15.

<sup>1086</sup> Deposition Lindsay Burckhalter, August 11, 2023, *Cobb County v. Purdue Pharma et al.*, Case No. 1:18-op-45817-DAP. In *Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), (hereinafter “Burckhalter Dep.”), at 173:14-21; Brice Dep. at 335:6-335:13. See Deposition of Erika Owens, July 28, 2023, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. In *Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), at 221:1-9 (Publix pharmacist in Cobb County testified she does not document clearing red flags).

<sup>1087</sup> Deposition of Katherine Leonard, December 2, 2022, *Cobb County v. Purdue Pharma et al.*, Case No. 1:18-op-45817-DAP. In *Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), (herein after “Leonard Dep.”), at 27:2-7.

additional feedback in a note by one pharmacist, I don't want that to be automatically applied and affect the judgment of the next pharmacist because the pharmacist claims X, Y or Z about a patient. I want it to be the individual judgment of a pharmacist. So I am not opposed to documentation. It's not a requirement. I still emphasize the fact that a trained professional pharmacist has the ability to have a conversation with the patient and arrive at those decisions and without a requirement of documenting every detail of that conversation that led them to their decision to fill or not."<sup>1088</sup>

- ix. In fact, documentation of red flags and their resolution, or lack thereof, is crucial for pharmacists to be able to communicate with one another to identify suspicious patterns that may only become apparent after identifying a patient customer's or prescriber's behavior across several different encounters with different pharmacists and pharmacies.
- x. Even when Publix learned of a prescriber issuing illegitimate prescriptions, it made no systemic effort to inform its pharmacists. "[A]s far as Publix pharmacy issuing a statement on a physician, I have not seen that occur."<sup>1089</sup> Although it was possible for pharmacists to create notes about a particular prescriber, doing so was not required.<sup>1090</sup> There was no uniform practice regarding where in the system such notes would be placed, and no system to alert pharmacists that such notes even existed.<sup>1091</sup> Equally troubling, these notes could be deleted.<sup>1092</sup> Further, in order to see the notes, the pharmacist would have had to 'click' on the prior encounter to open it,<sup>1093</sup> an extra step that requires more time and is disincentivized by Publix bonus strategy, which pays pharmacists more if they fill more prescriptions, including for controlled substances. Publix could have eliminated most of these problems by creating a system for easy tracking of red flags across patient customers and providers through time, which they did not do.
- xi. Publix created a Pharmacy Advocacy Team in 2020 ostensibly to facilitate feedback from its stores to corporate leadership.<sup>1094</sup> In 2021, however, one of the pharmacist members on the team sought "Corporate lead guidance" regarding the need to "[e]ducate and re-

<sup>1088</sup> Leonard Dep. at 244:7-245:10.

<sup>1089</sup> Deposition of Leigh Anne Jacobson, November 8, 2022, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), at 313:9-18.

<sup>1090</sup> Deposition of Chris Hewell, October 7, 2022, *Cobb County v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), (hereinafter "Hewell 30(b)(6) Dep."), at 263:14-19.

<sup>1091</sup> Hewell 30(b)(6) Dep. at 302:18-304:7; 305:3-308:8; 315:16-316:16.

<sup>1092</sup> Hewell 30(b)(6) Dep. at 310:16-311:23; PUBLIX-MDLT8-00149649 at \*10.

<sup>1093</sup> Hewell 30(b)(6) Dep. at 101:3-14 and 304:23-305:22.

<sup>1094</sup> PUBLIX-MDLT8-00115907.



educate on Corresponding Duty, Proper filling standards on controlled substances, how to professionally communicate refusals to fill, proper documentation in EnterpriseRx, uniform refill policy of controlled substances, mandatory Narcan counseling, acceptance of coupons and/or GoodRx, updated R&P guide with more concrete policy. Help and assistance in this areas is one of the most common complaints I received. **(Dain)**<sup>1095</sup> Publix failed to provide the requested guidance.<sup>1096</sup> The “first and only meeting of the opioid task force” was in 2021, and the task force was thereafter “disbanded” because Ms. Leonard “didn’t see the need to continue.”<sup>1097</sup>

- xii. Publix knew that some of the opioids it dispensed were being diverted. For example, in January 2020, Pharmacy Supervisor Mike Chavez learned of a fraudulent prescription presented at a Publix Store in Cobb County.<sup>1098</sup> Investigation by the Compliance Department uncovered twelve additional prescriptions Publix had sold in Cobb County that had been written by the same prescriber.<sup>1099</sup> Compliance also found that at least six of those fraudulent prescriptions had been filled despite notes in Publix’s dispensing system that would have alerted the pharmacies to the fraudulent prescriptions if the pharmacists had looked at them, which they evidently failed to do.<sup>1100</sup>
- xiii. As of August 11, 2023—the date of the Burckhalter deposition—Publix (i) did not have any checklist for red flag analysis,<sup>1101</sup> (ii) did not have a centralized system for tracking red flags and refusals to fill controlled substance prescriptions,<sup>1102</sup> (iii) did not require documentation of red flags.<sup>1103</sup> Further, despite acknowledging that PDMPs are one of the most effective tools in preventing diversion of controlled substances, Publix still does not require its pharmacists to check PDMPs prior to dispensing controlled substances unless the state where they are practicing mandates it.<sup>1104</sup> Publix was aware that for Publix pharmacists

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<sup>1095</sup> PUBLIX-MDLT8-00115817 at -115820 (emphasis in original). The team included pharmacists and, among others, Publix’s VP of Pharmacy Dain Rusk and Director of Retail Pharmacy Operations Kathy Leonard. PUBLIX-MDL8-00115907.

<sup>1096</sup> PUBLIX-MDLT8-00083775 at 83780.

<sup>1097</sup> Leonard Dep. at 202; 207-08.

<sup>1098</sup> Deposition of Michael Chavez, December 14, 2022, *Cobb County v. Purdue Pharma, et al.*, Case No. 1:18-op-45817-DAP. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8), (hereinafter “Chavez Dep.”), at 312:24-316:4. PUBLIX-MDLT8-00077925.

<sup>1099</sup> PUBLIX-MDLT8-00077925 at -779276.

<sup>1100</sup> Chavez Dep. at 316:18-317:9, 320:13-321:1; PUBLIX-MDLT8-00077925 at -779276.

<sup>1101</sup> Burckhalter Dep. at 171:1-171:17; 147:8-148:6.

<sup>1102</sup> Burckhalter Dep. at 171:18-172:21.

<sup>1103</sup> Burckhalter Dep. at 172:22-173:21.

<sup>1104</sup> Smith Dep. at 369:15-369:21.

in Georgia, it was “not the norm” to check the PDMP before dispensing controlled substances.<sup>1105</sup>

- xiv. Also as of August 11, 2023, at Publix, the more controlled substances filled, the more money pharmacists and pharmacy team members earn,<sup>1106</sup> because controlled substances are still included when calculating script count, volume, or store profitability measures for the purposes of pharmacist bonus calculations.<sup>1107</sup> These types of financial incentives to dispense more prescriptions inherently conflict with the need to detect and resolve red flags.
- xv. From May 2006 through May 2019, Publix filled 752,246 opioid prescriptions, representing 31,789,759 dosage units, to Cobb County residents. According to Plaintiff’s red flag analysis, of those, 337,882 prescriptions triggered at least one red flag; 140,276 triggered at least two red flags; 57,550 triggered at least three red flags; and 23,048 triggered at least four red flags.<sup>1108</sup>
- q. In summary, the Pharmacy Defendants were far more than unwitting pill , dispensers. Instead, they actively participated in efforts to increase the opioid supply while ignoring the many warning signs of a growing opioid problem, and as such were central drivers of the opioid epidemic. As the “last line of defense” against opioid misuse and diversion, these Defendants failed miserably.

**7. No reliable scientific evidence shows that long-term opioid therapy is effective for chronic non-cancer pain.**

- a. Through the aforementioned methods, and by relying on flawed and industry-backed studies, the Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree.
- b. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the “undertreatment of pain.” Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due

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<sup>1105</sup> PUBLIX-MDLT8-00074321.

<sup>1106</sup> Burckhalter Dep. at 176:19-176:24.

<sup>1107</sup> PUBLIX-MDLT8-00059249.

<sup>1108</sup> Plaintiff’s CT8 Amended and Superseding Red Flag Analysis served September 19, 2023, pursuant to Section D.2 of CMO.

to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk.<sup>1109</sup> Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving the pain of opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. A detailed table and a summary demonstrative, below, summarize the lack of reliable evidence that prescription opioids are effective for chronic pain:

Study	YEAR	TYPE OF PAIN	LACK OF EVIDENCE
<b>Chou R, et al.</b> , Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. <i>Journal of Pain</i> . 2009;10(2):113-130 at p. 130.e5.	2009	Chronic non-cancer pain	“insufficient to assess effects on health outcomes”
<b>Noble M., et al.</b> Long-term opioid management for chronic noncancer pain. <i>Cochrane Database Syst Rev</i> . 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.	2010	Chronic non-cancer pain	“weak” evidence  “Whether quality of life or functioning improves is inconclusive.”
<b>Chaparro LE, et al.</b> Opioids compared to placebo or other treatments for chronic low-back pain. <i>Cochrane Database Syst Rev</i> . 2013. doi:10.1002/14651858.CD004959.pub4	2013	Chronic low-back pain	“does not support that opioids are more effective than other groups of analgesics”
<b>da Costa BR, et al.</b> Oral or transdermal opioids for osteoarthritis of the knee or hip <i>Cochrane Database Syst Rev</i> . 2014	2014	Osteoarthritis pain (knee or hip)	“may have deleterious effects and do not seem to improve pain relief”
<b>Chou. R., et al.</b> The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. <i>Ann Intern Med</i> . 2015;162(4). doi:10.7326/M14-2559, at p. 276	2015	Chronic pain	“Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function.”
<b>Krebs EE., et al.</b> Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. <i>JAMA - J Am Med Assoc</i> . 2018. doi:10.1001/jama.2018.0899	2018	Chronic back pain; Osteoarthritis pain (knee or hip)	“no benefit of opioids over non-opioid medication”
<b>Welsch P, et al.</b> Opioids in chronic noncancer pain—are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. <i>Schmerz</i> . 2015. doi:10.1007/s00482-014-1436-0, at p. 3.	2015	Chronic low-back pain	“weak evidence”
<b>Sandbrink, F., et al.</b> (2023). The Use of Opioids in the Management of Chronic Pain: Synopsis of the 2022 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline. <i>Annals of Internal Medicine</i> , 10.7326/M22-2917. <a href="https://doi.org/10.7326/M22-2917">https://doi.org/10.7326/M22-2917</a> , at p. 394.	2023	Chronic pain	“The benefits that opioids can provide are small and are outweighed by the risks to the patient.”

<sup>1109</sup> As stated in the NASEM 2017 Report, “The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but it would be a mistake to infer that greater utilization of opioids would ameliorate these problems,” due to the lack of evidence that opioids provide long-term benefits for chronic pain. NASEM Report (2017), fn. 58, above, at p. 51. (emphasis added).

<b>Bonnie, R. et al.</b> Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. NASEM. 2017. Washington, DC: The National Academies Press. doi: <a href="https://doi.org/10.17226/24781">https://doi.org/10.17226/24781</a>	2017	Long-term pain	<b>"lack of evidence that the drugs are effective for long-term pain management"</b>
<b>Busse JW, et al.</b> Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. <i>JAMA</i> . 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472	2018	Chronic pain	<b>Failure to meet test of Minimally Important Difference in pain relief compared to placebo; no difference between opioids and non-opioids for pain relief.</b>



- c. As summarized in the tables above, scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."<sup>1110</sup> Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:

- i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy,

<sup>1110</sup> Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*. 2009;10(2):113-130 at p. 130.e5.

decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.<sup>1111</sup>

Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks, months, or years to manifest, and duration of exposure is the most significant risk factor for addiction (*see* discussion of Edlund study, above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers (the molecular equivalent of heroin) requires a longer period of study than 12 weeks.

- ii. According to a study of combat injury victims among military personnel, 6.8% developed an opioid addiction after a short-term prescription of opioids (within a 7-day discharge window). The median time to diagnosis of the opioid use disorder was 3 years.<sup>1112</sup> The authors state that this was “the first study to show that persistent opioid use after trauma is associated with the development of clinically recognized opioid abuse years after the initial injury.”<sup>1113</sup> The long median time to diagnosis of opioid addiction reinforces the conclusion that industry-sponsored studies claiming a low risk of addiction are far too brief to provide reliable, real-world estimates of risk.<sup>1114</sup>
- iii. Naliboff *et al.*, in their two-arm, randomized, pragmatic clinical trial comparing stable dose to escalating dose of opioid medications among 135 patients at a VA clinic in Los Angeles, “carefully selected” as appropriate candidates for chronic opioid therapy, nevertheless discharged 27% of patients over the course of the study due to opioid misuse/noncompliance.<sup>1115</sup> Urine toxicology screens were included in the protocol.<sup>1116</sup> The authors concluded, “Overall, this study confirms that even in carefully selected tertiary-care patients, substance misuse is a significant problem. Importantly, *40% of these misuse problems did not become apparent within the first 6 months, pointing out the need for studies of longer duration.*”<sup>1117</sup> (emphasis added). These data also

<sup>1111</sup> Matthias M, Donaldson MT, Jensen AC, Krebs EE. “I was a little surprised”: Qualitative Insights from Patients Enrolled in a 12-Month Trial Comparing Opioids to Non-Opioid Medications for Chronic Musculoskeletal Pain. *J Pain*. 2018; 1-9, at p. 1.

<sup>1112</sup> Beyer CA, Poltavskiy E, Walker LE *et al.*, Persistent Opioid Use After Combat Injury and Subsequent Long-term Risk of Abuse: a retrospective cohort study. *Annals of Surgery*, 2019; 1-9, at p. 1.

<sup>1113</sup> *Id.* at p. 3.

<sup>1114</sup> *See* discussion of industry-sponsored studies of addiction risk at Section §C.8, below.

<sup>1115</sup> Naliboff BD, Wu SM, Schieffer B, *et al.* A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*. 2011;12(2):288-296, at p. 288.

<sup>1116</sup> *Id.* at p. 291.

<sup>1117</sup> *Id.* at p. 295.



support the need for ongoing monitoring for misuse and addiction in patients prescribed opioids long-term.

- iv. There are serious and certain risks associated with long-term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia (increased pain caused by opioids), immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long-term opioid therapy.<sup>1118</sup> These risks increase with increasing dose and duration of the drug.<sup>1119</sup> Hence, the high risks associated with opioids necessitate a longer study period to assess the true benefit-to-risk ratio for all patients.
- d. A series of reviews, including several in the Cochrane Database, a collection of reviews that summarize the results of medical research, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.
  - i. The 2010 Cochrane Review (Noble 2010) found that there was only “weak” evidence to support the use of opioids for chronic non-cancer pain.<sup>1120</sup>
    - A. “All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias.” Reasons for this assessment included the funding source (“Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (*e.g.*, drug company),” failure to compare characteristics of dropouts to those of patients who completed the studies, and failure to describe recruitment methods. The highest risk of bias existed for the “continuous outcomes” of pain relief and quality of life, because “high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes.”<sup>1121</sup>

<sup>1118</sup> Lembke *et al.*, “Weighing The Risks,” fn.5, above, at p. 985; *see also* Chou, “Effectiveness and Risks”, fn. 414, above, at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. *JAMA Internal Medicine*. 2018, at p. 298.

<sup>1119</sup> Chou R, Turner JA., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162(4). doi:10.7326/M14-2559, p. 283.

<sup>1120</sup> Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.

<sup>1121</sup> *Id.* at pp. 7-8.



- B. At pp. 9-14, specific data on attrition were provided: For the “strong opioid” category (categories described at p. 7), including extended release morphine, controlled release oxycodone, extended release oxymorphone, extended release tramadol and methadone; for oral medications, 34.1% discontinued due to adverse effects<sup>1122</sup> and 10.3% discontinued due to insufficient pain relief,<sup>1123</sup> for a total of 44.4% who discontinued strong oral opioids.<sup>1124</sup> Almost half of all study participants dropped out of the study before it was complete, yet their data was not included in the final analyses.
- C. The review states that only 273 (58%) of those who began the long-term extensions of short-term trials remained in the study at the 6-7.5 month cut-off point where data were available for all three oral opioid studies. “Because the attrition rate is so high, the participants are likely highly selected, and the data may be biased.”<sup>1125</sup>
- D. The authors report pain relief for those able to remain on oral opioids for six months; however: “The strength of the evidence supporting this conclusion is weak.”<sup>1126</sup>
- E. Quality of Life (QoL):
  - I. For oral morphine: A single study (Allan, 2005), reporting a “small improvement on the mental subscale and a larger improvement of the physical subscale” provided an “insufficient quantity of data from which to draw conclusions.”<sup>1127</sup>
  - II. QoL improvement was “weakly supported” with transdermal fentanyl (TDF).<sup>1128</sup> For QoL with intrathecal opioids, there were inconsistent findings “No conclusions can be drawn.”<sup>1129</sup>
- F. “Data describing long-term safety and efficacy of opioids for CNCP [chronic non-cancer pain] are limited in terms of quantity and quality. An evidence base consisting of low-

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<sup>1122</sup> *Id.* at p. 10

<sup>1123</sup> *Id.* at p. 13.

<sup>1124</sup> *Id.* at pp. 9-14.

<sup>1125</sup> *Id.* at p. 15.

<sup>1126</sup> *Id.* at p. 16.

<sup>1127</sup> *Id.* at p. 20.

<sup>1128</sup> *Id.* at p. 21.

<sup>1129</sup> *Id.* at p. 22.

quality studies provides only *weak evidence* from which to draw qualitative conclusions and only low-stability evidence from which to draw quantitative conclusions.” (Emphasis added.)<sup>1130</sup>

- G. “Despite the identification of 26 treatment groups with 4,768 participants, the evidence regarding the effectiveness of long-term therapy in CNCP was too sparse to draw firm conclusions.”<sup>1131</sup>
- ii. Another Cochrane Review of opioids in the treatment of chronic low back pain (CLBP) (Chaparro 2013) found, “There is some evidence (*very low to moderate quality*) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo.”<sup>1132</sup> Yet the authors make clear there is little or no evidence of opioid efficacy long-term.
  - A. “There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP . . . . We have no information from randomized controlled trials supporting the efficacy and safety of opioids used for more than four months. Furthermore, the current literature does not support that opioids are more effective than other groups of analgesics for LBP such as anti-inflammatories or anti-depressants.”<sup>1133</sup>
  - B. “The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management

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<sup>1130</sup> *Id.* at p. 23.

<sup>1131</sup> *Id.* at p. 25.

<sup>1132</sup> Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD004959.pub4, at p. 2. (emphasis in original) A recent Cochrane Review by Cashin, et al [Cashin AG, *et al.* Pharmacological treatments for low back pain in adults: An overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2023;4(4):CD013815.] suggests that there may be some small benefit of opioids for chronic pain. However, this review is subject to the same limitations cited elsewhere in this Report. In particular, the opioid portion of the Cashin review was based almost entirely on 12-week studies, providing no evidence of opioids’ efficacy for long-term use in chronic pain—the condition for which they were chiefly marketed; and the studies suffered from unacceptably high rates of attrition. The only opioid study cited by Cashin that was longer than 12 weeks was by Wild, *et al.*, the weaknesses of which are set forth at §C.7.d.iv.F. and footnote 1146 of this Report, including lack of blinding of the patients and investigators to treatment group, and lack of a placebo group for comparison. Cashin also relies on industry-sponsored studies that are well-known to suffer from bias.

<sup>1133</sup> Chaparro, “Opioids compared to placebo”, fn. 1132, above.

should be done with extreme caution, especially after a comprehensive assessment of potential risks.”<sup>1134</sup>

- iii. Another Cochrane review (McNicol 2013) found: “While intermediate term studies all indicated that opioids were better than placebo, most studies were small, most were short, and none used methods known to be unbiased. All these features are likely to make effects of opioids look better in clinical trials than they are in clinical practice.”<sup>1135</sup> Note that the McNicol review defined “intermediate” term studies as 35-84 days (*i.e.*, 5-12 weeks). Accordingly, these so-called intermediate studies are actually 12 weeks or less, therefore too brief to provide data relevant to efficacy for chronic pain, typically defined as lasting 12 weeks or more.<sup>1136</sup>
- iv. Another 2014 Cochrane Review reached similar conclusions: “Similar to previous systematic reviews of randomized trials on opioid therapy for non-cancer pain [cites omitted], we found that most of the trials included in our review had a treatment duration of several days or a few weeks only.”<sup>1137</sup>
  - A. “Although some of the newer trials in the update had slightly longer treatment durations [citations omitted], in none of the trials did the participants receive opioids for longer than six months. This is still too short to address the impact of opioid treatment on routine clinical practice in the treatment of a chronic condition such as osteoarthritis. While no evidence of long-term effects is available from randomized trials, observational studies indicate that long-term treatment with opioids of chronic conditions such as osteoarthritis may have deleterious effects and do not seem to improve pain relief [citation omitted].”<sup>1138</sup>
  - B. Reviewers found that the “small mean benefit” was “contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI [confidence

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<sup>1134</sup> *Id.*

<sup>1135</sup> McNicol E, Midbari A, Eisenberg E. Opioids for neuropathic pain (Review). *Cochrane Database Syst Rev.* 2013. doi:10.1002/14651858.CD006146.pub2, at p. 3

<sup>1136</sup> *Id.* at p. 13.

<sup>1137</sup> da Costa BR, Nuesch E, Kasteler R, *et al.* Oral or transdermal opioids for osteoarthritis of the knee or hip *Cochrane Database Syst Rev.* 2014, at p. 28.

<sup>1138</sup> *Id.*

interval] did not include the minimally clinically important difference” of 0.9 cm on a 10 cm visual analog scale.<sup>1139</sup>

- C. The 2014 Cochrane Review included studies of tapentadol, as well as several other opioids. In particular, a study of tapentadol by Afilalo, *et al.*, was among the studies as to which the Cochrane Review found too little evidence of benefit to justify the risk.<sup>1140</sup> Afilalo compared tapentadol ER 100-250 mg twice daily against placebo or oxycodone CR 20-50 mg twice daily.<sup>1141</sup> The primary, pre-specified endpoint of the study was changes from baseline Average Pain Intensity (API) as measured on an 11-point numerical rating scale (NRS).<sup>1142</sup> The Afilalo study was funded by Johnson and Johnson, and 9 of the 10 listed authors were employed by either J&J or Grunenthal (the German entity that developed tapentadol).<sup>1143</sup>
- D. To correctly interpret the results of an efficacy study, it is important to distinguish between “statistical significance,” a numerical calculation, and “clinical significance,” which addresses the question of whether a patient experiences a noticeable beneficial difference with the treatment under investigation. Contrary to the practice of setting a pre-specified, “minimal clinically important difference” by which to assess relevant changes, as described in the Cochrane review (above), the Afilalo study did not establish such a standard. Instead, the authors reported “statistically significant” reduced average pain intensity for tapentadol compared to placebo, although the API difference between tapentadol and placebo was only 0.7 cm,<sup>1144</sup> which fails to meet the test of a minimally clinically important difference. That this study failed to mention the lack of a *clinically* significant difference between tapentadol and placebo for the

<sup>1139</sup> *Id.* at p. 2. Some authors have endorsed a “Minimal Important Difference” of 1.0 cm rather than 0.9 cm on the 10 cm VAS. *See e.g.*, Busse JW, Wang L, Kamaleldin M. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *JAMA*. 2018;320(23):2448-2460. doi:10.1001/jama.2018.18472. In either case, the salient point is that opioid therapy generally does not meet even this minimal threshold of efficacy in randomized clinical trials, which makes the extraordinary risks of opioid therapy all the more unacceptable.

<sup>1140</sup> da Costa, “Oral or transdermal” fn. 1137, above, at p. 15.

<sup>1141</sup> Afilalo M, *et al.* Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee *Clin. Drug Investig* 2010; 30:489-505.

<sup>1142</sup> Tapentadol (CG5503), Clinical Trials.Gov (last updated Apr. 18, 2012), <https://clinicaltrials.gov/ct2/show/NCT00421928>.

<sup>1143</sup> Afilalo, “Efficacy and Safety”, fn. 1141, above, at p. 503.

<sup>1144</sup> *Id.* at p.489.

primary, prespecified endpoint, suggests the possibility of bias in reporting.<sup>1145</sup>

- E. In 2015, Janssen and Grunenthal funded a study by Buynak *et al* purporting to evaluate the long-term efficacy of tapentadol ER among subjects with osteoarthritis or low back pain, who had completed one of four underlying, manufacturer-sponsored studies, one of which was the Afilalo study described above.<sup>1146</sup> The Buynak 2015 article does not state that the underlying studies failed to meet the accepted standard for a Minimally Important Difference from placebo (Afilalo 2010, -0.7 cm; Buynak 2010, -0.8 cm; Lange 2010, -0.6 cm).
- F. As noted in the Cochrane Review (2010), above, the highest risk of bias occurs in opioid studies for the “continuous outcomes” such as pain relief because high attrition rates affect the risk of bias and the generalizability of the results. The tapentadol studies described above suffer from such bias, in that (1) the underlying studies all experienced significant dropout rates (only 57.3%, 52.2%, 56.5% and 46.2% of the tapentadol subjects completed the Afilalo, Buynak 2010, Lange, and Wild studies, respectively); and (2) only 60.5% of the subjects completed the study analyzed in the 2015 Buynak article,<sup>1147</sup> even though the population that entered the latter study consisted of the subset of subjects who had successfully completed the prior trials. In each study, adverse events and lack of efficacy were leading reasons for failure to complete the study.

- v. Chou *et al.* in their 2015 systematic review on the effectiveness of opioids in the treatment of chronic pain stated: “Evidence is *insufficient*

<sup>1145</sup> The authors emphasized a claim of “clinical” significance based on a statistically significant result for one of six secondary endpoints, that is, the proportion of subjects reporting more than 50% improvement in pain intensity from baseline. <https://clinicaltrials.gov/ct2/show/NCT00421928>. However, the Afilalo study made no adjustment to impose a more strict test of significance due to testing of multiple endpoints.

<sup>1146</sup> Buynak R *et al.*, Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. *Clin. Ther.* 2015; 37:2420-2438. In addition to the Afilalo study, the Buynak (2015) article analyzed data for patients from prior manufacturer-sponsored studies by Buynak R. *et al.* Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo-and active-controlled phase III study. *Expert Opin. Pharmacother.* 2010; 11:1787-1804; Lange B, *et al.*, Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv. Ther* 2010; 27:381-399; Wild JE, *et al.* Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Practice* 2010; 10:416-427. The Wild study did not include a placebo group and thus provided no data regarding difference in average pain intensity between tapentadol and placebo.

<sup>1147</sup> Buynak, “Long-term safety”, fn. 1146, above, at p. 2424.

to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.”<sup>1148</sup> The authors reported that most placebo-controlled studies were less than 6 weeks, and none were over 16 weeks long. “We did not include uncontrolled studies for these outcomes; reliable conclusions cannot be drawn from such studies because of the lack of non-opioid comparison group and heterogeneity of the results.”<sup>1149</sup>

- vi. In 2009, Chou was the lead author of a panel made up of a majority of Industry-funded physicians and psychologists who promulgated Guidelines that allowed for the use of chronic opioid therapy; in the same publication, those authors admitted that evidence regarding chronic opioid therapy was of “low quality,” meaning that it was “insufficient to assess effects on health outcomes.”<sup>1150</sup> There are several other important aspects to this particular publication. First, despite the insufficient evidence, the article made a “strong” recommendation to initiate opioid therapy for chronic noncancer pain, and the strength of the recommendation was contradictory to the weakness of the evidence. Second, the recommendation to initiate opioid therapy appeared in the summary “abstract” on the first page of the article, where it would be seen by even a casual review, while the weakness of the evidence appeared only in a “supplement” to the main article that would have required a diligent search to discover. Third, the article purported to state “Guidelines” of professional medical societies, the American Pain Society and the American Academy of Pain Medicine, giving the recommendations an undeserved sheen of authority. Finally, the article did not disclose that both APS and AAPM were funded by large contributions from the manufacturers of opioids who stood to profit from their sale and use pursuant to the recommendations in the article.
- vii. In another, later systematic review of opioid and non-opioid medication for acute or chronic low back pain, Chou *et al.* found that evidence for opioids “remains limited to short term trials showing modest effects versus placebo for chronic low back pain.”<sup>1151</sup> Shortcomings of the studies included high attrition (30-60% in most trials) and “short follow-up” (one at 16 weeks, all others shorter).<sup>1152</sup> Authors also noted: “Trials were not designed to assess the risk for overdose or opioid use

<sup>1148</sup> Chou. “Effectiveness and Risks -Systematic Review”, fn. 1119, above, at p. 276 (emphasis added.)

<sup>1149</sup> *Id.* at p. 280.

<sup>1150</sup> Chou, *et al.*, “Clinical Guidelines,” fn.340, above, at p. 130.e5.

<sup>1151</sup> Chou R, Deyo R, Friedly J, *et al.* Systemic pharmacologic therapies for low back pain: A systematic review for an American College of physicians clinical practice guideline. *Ann Intern Med.* 2017. doi:10.7326/M16-2458, at p. 480.

<sup>1152</sup> *Id.* at p. 483



disorder because of relatively small samples, short follow up, and exclusion of higher risk patients; in addition, many studies used an enriched enrollment randomized withdrawal design which could underestimate harms.”<sup>1153</sup> (See §C.7.e, below, for discussion of enriched enrollment study design).

- viii. In a systematic review and meta-analysis (Häuser, *Schmerz*, 2015) of open-label continuation trials up to 26 weeks in duration in patients with a variety of different chronic pain disorders, the authors state “... the risk of bias [for these studies] was high ... all studies were funded by the manufacturers of the drugs<sup>1154</sup> . . . . average pain scores are unrepresentative of patient experience and of very limited utility<sup>1155</sup> .... The positive effects of opioid in long-term open-label studies cannot be disentangled from those of co-therapies not controlled for, from unspecific (placebo) effects because of the lack of placebo group or from the spontaneous recovery because of the lack of no treatment group. The external validity of open-label extension studies was comprised [sic] by a highly selected group of patients without major medical disease or mental disorders. The self-selected group of patients who were willing to participate in the open-label extension studies does not permit a clear conclusion on the long-term efficacy of opioids in routine clinical care.”<sup>1156</sup>
- ix. At a 2001 Janssen Scientific Advisory Board, while discussing how to promote Janssen’s fentanyl patch, Duragesic, the consensus statements made it clear that funding for research would be contingent on getting results favorable to Duragesic: “If a pilot pans out we may increase funding to expand the study.”<sup>1157</sup> And “The goals for EMRP studies should be explicitly stated: Janssen wants to obtain certain data and seed studies that, after completion, may be expanded by funding from other sources.”<sup>1158</sup> This is indicative of the types of bias that can arise from industry-funded studies.
- e. Many studies used an enriched enrollment randomized withdrawal (EERW) study design, an inherently biased methodology which *a priori* favors opioids over placebo. EERW design selects patients who are predisposed to tolerate

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<sup>1153</sup> *Id.* at pp. 486-487.

<sup>1154</sup> Häuser W, Bernardy K, Maier C. Long-term opioid therapy in chronic noncancer pain: A systematic review and meta-analysis of efficacy, tolerability and safety in open-label extension trials with study duration of at least 26 weeks. *Schmerz*. 2015. doi:10.1007/s00482-014-1452-0, at p. 4.

<sup>1155</sup> *Id.* at p. 7

<sup>1156</sup> *Id.* at p. 8.

<sup>1157</sup> JAN-MS-00481055 at -1056

<sup>1158</sup> *Id.* at -1057.

and prefer opioids, and hence are not reflective of the general clinical population.

- i. Randomized, double blind, placebo-controlled trials of 12 weeks durations or less (15 studies total) of opioids in the treatment of chronic pain used to get FDA approval, relied on enriched enrollment design (Meske *et al.* 2018),<sup>1159</sup> and hence were biased toward favoring opioids. Open-label continuation trials commonly included subjects who successfully completed the randomized controlled trial phase using an enriched enrollment design. Hence those who entered the open label phase included those who successfully tolerated opioids through the randomized controlled trial period, resulting in an additional layer of bias favoring opioids, and diminishing the applicability of the study results to real world conditions.
- ii. For example, of the 295 initial subjects in the study by Caldwell *et al.* (2002) 222 subjects were assigned to opioid groups and 73 were assigned to placebo.<sup>1160</sup> A 4-week randomized controlled trial (RCT) preceded an open-label phase; 40% of the opioid group who participated in the RCT dropped out due to adverse effects or inadequate pain relief,<sup>1161</sup> and only those who lasted the full four weeks were permitted to enter the open-label phase. Of the 184 subjects who entered the open-label phase, 131 (72%) came from the opioid groups, while only 50 (28%) came from the placebo group; therefore, the open-label phase included a large majority of subjects who had demonstrated the capability to tolerate opioids, and the study's claims of efficacy are not transferable to a real-world population. Despite the bias favoring opioid-tolerant subjects, more than half failed to complete the open-label phase; 95/181 (52.5%) discontinued.<sup>1162</sup>
- iii. A meta-analysis of short term studies (< 6 weeks) confirmed a difference between enriched enrollment studies and non-enriched enrollment studies in terms of adverse medical consequences: "The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the

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<sup>1159</sup> Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *J Pain Res.* 2018. doi:10.2147/JPR.S160255, at pp. 923-934.

<sup>1160</sup> Caldwell JR, Rapoport RJ, Davis JC, *et al.* Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002. doi:10.1016/S0885-3924(02)00383-4, at p. 283.

<sup>1161</sup> *Id.* at p. 283.

<sup>1162</sup> *Id.* at p. 286.

number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported.”<sup>1163</sup>

- f. A recent (Busse 2018) meta-analysis confirms that there are no data to show clinically significant long-term efficacy of opioids in the treatment of chronic pain.<sup>1164</sup>
  - i. The primary study outcomes were “pain relief, physical functioning, and vomiting.”<sup>1165</sup> The study defined the term Minimally Important Difference (MID) as “the smallest amount of improvement in a treatment outcome that patients would recognize as important.”<sup>1166</sup> The data showed that opioid therapy failed to meet the MID as to the primary outcomes of pain relief and physical functioning, as well as the secondary outcomes of emotional functioning, social functioning, or sleep quality compared to placebo.<sup>1167</sup>
  - ii. For pain relief, the MID was defined as 1 cm on the 10 cm Visual Analog Scale (VAS); the data showed that the difference between opioid therapy and placebo was only 0.79 cm on the VAS, thus no minimally important difference was shown.<sup>1168</sup> Despite not meeting the standard, the authors state, “Although the difference did not meet the minimally important difference of 1 cm, opioids were associated with pain relief compared to placebo . . . .”<sup>1169</sup> A more accurate statement would be that opioids were associated with a clinically insignificant difference in pain relief, since the change did not meet the study’s own definition of a clinically significant difference. The study reported a difference of 2.80 favoring opioids over placebo on a 100-point scale for “role functioning;” however, “[w]hen restricted to trials reporting actual change, high quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared to placebo.”<sup>1170</sup>
  - iii. For the primary endpoint of vomiting, the opioid subjects had more than a 4-fold greater risk in nonenrichment trials, and a 2.5 times

<sup>1163</sup> Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag.* 2011;16(5):337-351. doi:10.1155/2011/465281, at p. 347.

<sup>1164</sup> Busse, “Opioids for Chronic Noncancer Pain”, fn. 1139, above.

<sup>1165</sup> *Id.* at p. 2449.

<sup>1166</sup> *Id.* at p. 2450.

<sup>1167</sup> *Id.* at pp. 2451, 2455.

<sup>1168</sup> *Id.* at p. 2451.

<sup>1169</sup> *Id.* at pp. 2451-2452.

<sup>1170</sup> *Id.* at pp. 2451, 2455.

greater risk in enrichment trials, that is, trials in which subjects were pre-selected for greater ability to tolerate opioid therapy.<sup>1171</sup>

- iv. As for “Active Comparator” studies, the authors state: Moderate quality evidence [9 RCTs, 1431 patients] showed “no difference in the association of opioids versus nonsteroidal anti-inflammatory drugs for pain relief,” and the same was true for physical function. The only significant difference was over 4-fold greater vomiting with opioids compared to NSAIDs (RR = 4.74,  $p \leq 0.001$ ).<sup>1172</sup>
- v. Although the goal was to assess “chronic” non-cancer pain, the authors acknowledge that “it was not possible to assess the long-term associations of opioids with chronic non-cancer pain because no trial followed up patients for longer than 6 months.”<sup>1173</sup> There is some inconsistency in the literature about the definition of “chronic.” For example, the Cochrane Review (Noble, 2010) cites the International Association for the Study of Pain (IASP) for a definition of “pain which persists past the normal point of healing,” considered to be 3 months;<sup>1174</sup> however, on the very next page, the Cochrane review states that it considered only studies of at least six months, which it termed “Chronic opioid use.”<sup>1175</sup> In any case, the Busse authors’ statement that it could not be applied to “long-term” use is an important limitation.
- vi. The Busse study states, “Studies with longer follow-up reported less relief,” which provides significant support for the reduced pain relief of opioids over time, and which buttresses the conclusion that even the minor “improvements” in pain and physical function shown in the studies compiled by Busse, which had a median of only 60 days’ follow-up,<sup>1176</sup> cannot be extrapolated to longer term opioid use.
- vii. Over three-quarters of the studies (79%) reported receiving industry funding.<sup>1177</sup>
- viii. Despite these limitations, the authors concluded: “... some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids.” The figure of 12% appears to represent the difference between the percentage who reported MID pain relief on placebo (48.7%) and

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<sup>1171</sup> *Id.* at p. 2455.

<sup>1172</sup> *Id.*

<sup>1173</sup> *Id.* at p. 2457.

<sup>1174</sup> Noble, *et al.*, “Long Term Opioid Management,” fn.1120, above, at p. 2.

<sup>1175</sup> *Id.* at pp. 3, 6.

<sup>1176</sup> Busse, *et al.*, “Opioids for Chronic Noncancer Pain,” fn. 1139, above, at p. 2451.

<sup>1177</sup> *Id.* at p. 2451.

those who reported MID pain relief on opioid therapy (60.6%); difference = 11.9%.<sup>1178</sup>

- ix. In sum, the Busse analysis stands for the proposition that, by submitting to opioid therapy, the patient incurs significant and potentially fatal risks, in exchange for “benefits” that are found to be comparable to placebo for the large majority of subjects studied.
- x. The pain relief MID standard adopted in the Busse study was at the low end of the spectrum of such study definitions, meaning that less improvement was required to meet the MID standard. A pooled analysis of multiple pain studies found that the average MID was 17 mm (1.7 cm) on the VAS scale, or over twice the 0.79 cm difference reported in the Busse meta-analysis.<sup>1179</sup> Despite the lenient standard to show a difference that patients would notice, the Busse results failed that test.
- xi. In 2022, Busse (2018) was cited by the U.S. Department of Veterans Affairs and U.S. Department of Defense in their updated clinical practice guidelines on the use of opioids in the management of chronic pain to support the finding that opioid therapy provided no clinically significant improvement in pain or physical function.<sup>1180</sup>
- g. The SPACE randomized clinical trial study, published in JAMA in 2018, comparing opioid and non-opioid medication in the treatment of chronic pain, is the first long-term (one year) randomized controlled trial of opioids in the treatment of moderate to severe pain, and found no benefit of opioids over non-opioid medication.<sup>1181</sup>
- i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to

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<sup>1178</sup> *Id.* at p. 2456.

<sup>1179</sup> Olsen MF, Bjerre E, Hansen MD, *et al.* Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med.* 2017. doi:10.1186/s12916-016-0775-3, at p. 10.

<sup>1180</sup> Sandbrink, F., Murphy, J. L., Johansson, M., Olson, J. L., Edens, E., Clinton-Lont, J., Sall, J., Spevak, C., & VA/DoD Guideline Development Group (2023). The Use of Opioids in the Management of Chronic Pain: Synopsis of the 2022 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline. *Annals of Internal Medicine*, 10.7326/M22-2917. Advance online publication. <https://doi.org/10.7326/M22-2917>, at p.389.

<sup>1181</sup> Krebs EE, Gravely A, Nugent S, *et al.* Effect of opioid vs non-opioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain the SPACE randomized clinical trial. *JAMA - J Am Med Assoc.* 2018. doi:10.1001/jama.2018.0899.

severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.<sup>1182</sup>

- ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long-term opioid therapy in real-life.<sup>1183</sup> Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.<sup>1184</sup> It was not sponsored by an opioid manufacturer.<sup>1185</sup>
- iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable.
- iv. Some patients in the non-opioid group received Tramadol, an opioid, leading to questions about the claim that non-opioids were equally effective. The number of patients receiving Tramadol was small, and Tramadol was administered as a second or third line rescue medicine, to simulate how it might be used in real-life clinical practice. The authors re-ran the data without the patients who were given Tramadol, and the results were “unchanged: over 12 months, pain-related function did not differ between groups ( $P=.19$ ) and the nonopioid group had better pain intensity ( $P=.01$ ).”<sup>1186</sup> Krebs, *et al.*, also state, “Although both groups improved, we concluded results did not support opioid initiation for chronic back pain or osteoarthritis pain because opioids

<sup>1182</sup> *Id.* at p. 872. The authors also reported that there was no significant difference between opioids and non-opioids for a secondary endpoint consisting of hospitalizations, emergency department visits and falls; and no significant difference in drug abuse or misuse (Table 3; pp. 878-879.) Neither of these findings is surprising in light of the relatively low doses of opioids (mean 21-28 MME) and the small population of 119 opioid-exposed subjects. See Supplementary Online Content, at Table e8.

<sup>1183</sup> *Id.* at p. 873.

<sup>1184</sup> *Id.* at p. 875.

<sup>1185</sup> *Id.* at p. 881.

<sup>1186</sup> Krebs EE *et al.*, In reply: opioids vs nonopioids for chronic back, hip or knee pain. *JAMA*. 2018;305(5): 508-509 at p. 509.



did not demonstrate any treatment advantages that offset their well-known risks of death and addiction.”<sup>1187</sup>

- h. A 2023 retrospective cohort study of chronic low back pain patients found that “treatment involving long-term opioid therapy over 12 months is not more effective in improving low back pain intensity, back-related disability or pain impact than treatment without opioids.”<sup>1188</sup>
- i. The opinion has been expressed, in a manufacturer-sponsored journal article and by defense experts in the opioid litigation, that a 3-month study is the “standard clinical trial duration accepted by the FDA for many chronic conditions.”<sup>1189</sup> However, the pre-approval choice of clinical study design and duration is made by the manufacturers themselves, not by the FDA, and some manufacturers have tested their pain medications in significantly longer randomized clinical trials against other pain relievers. For example, the VIOXX label indicates that VIOXX was tested in clinical trials of up to 86 weeks for osteoarthritis of the knee and hip, against ibuprofen;<sup>1190</sup> and the CELEBREX label states that CELEBREX was tested in clinical trials of up to 24 weeks in a rheumatoid arthritis population, as well as a 9-month clinical trial that revealed higher rates of complicated ulcers among patients taking CELEBREX plus aspirin for cardiac prophylaxis, compared to CELEBREX alone.<sup>1191</sup> Similarly, manufacturers of opioids could have conducted clinical trials of longer duration; if they had done so, it is likely that the results would have been comparable to those found by Krebs, that is, a higher risk of adverse events and no “treatment advantages” to offset those risks.<sup>1192</sup> Such early testing would have contradicted the promotion of opioids purported benefits and claims of low risks, which would have discouraged the widespread use of opioids and prevented the ensuing epidemic.
- j. Other studies have also shown that opioids are no better than non-opioids for pain treatment.
  - i. In the Cochrane Review by Chaparro, *et al.*, discussed above, opioids were not superior to non-opioids for chronic low back pain.<sup>1193</sup>

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<sup>1187</sup> *Id.*

<sup>1188</sup> Licciardone JC, *et al.* Effectiveness of long-term opioid therapy for chronic low back pain. *J Am Board Fam Med.* 2023;1-14, at pp. 8-9.

<sup>1189</sup> Meske, “Efficacy of opioids versus placebo”, fn. 1159, above, at pp. 923-924.

<sup>1190</sup> Vioxx label (2004), *see* [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2004/21647\\_vioxx\\_lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21647_vioxx_lbl.pdf) at p. 3

<sup>1191</sup> Celebrex label (2005), *see* [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/020998s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020998s017lbl.pdf) at pp. 4, 6-7

<sup>1192</sup> Krebs, “In reply”, fn. 1186, above, at p. 509.

<sup>1193</sup> Chaparro, *et al.*, “Opioids Compared to Placebo,” fn.1132, above, at p. 2.

- ii. In a review of randomized head to head comparisons of opioids versus non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12 weeks) therapy of neuropathic, low back, and osteoarthritic pain.<sup>1194</sup>
- iii. A systematic review comparing oral NSAIDs with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.<sup>1195</sup>
- k. The evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,<sup>1196</sup> was never more than "weak." Such "weak evidence" was never sufficient to justify the Pharmaceutical Opioid Industry's misleading messaging or the significant increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence<sup>1197</sup> that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.<sup>1198</sup> "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. According to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management*" (VonKorff *et al.*, 2011) (emphasis added).<sup>1199</sup>
- l. Evidence of the imbalance between significant risk and minimal benefit is reinforced by the studies demonstrating that significant numbers of pain patients will go on to long-term use of these addictive drugs, even with brief opioid exposure. Long-term exposure increases the risk of developing the disease of opioid addiction. "The majority of cases involving injury and death frequently occur with people using opioids exactly as prescribed, not just with those misusing or abusing them. Even more importantly, most studies indicate that patients on long-term opioid therapy are unlikely to stop even if analgesia and function are poor and safety issues arise. On the other hand, patients reporting pain relief and improvement in function with other modalities or

<sup>1194</sup> Welsch P, Sommer C, Schiltenswolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to non-opioid analgesics? : A systematic review and meta-analysis. *Schmerz*. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

<sup>1195</sup> Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthr Cartil*. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

<sup>1196</sup> Portenoy, Foley, "38 Cases", fn. 261, above.

<sup>1197</sup> Krebs *et al.*, "Effect of Opioid," fn. 1181, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn. 1194, above, at p. 3.

<sup>1198</sup> Krebs *et al.*, "Effect of Opioid," fn. 1181, above, at p. 880.

<sup>1199</sup> NASEM 2017 Report, at fn. 58, above, at p. 29.

surgical or non-surgical interventions continue to use opioids.”<sup>1200</sup> These findings emphasize the imbalance between significant risk and minimal benefit.

- m. The ASPPH Report concluded, “We urge that, consistent with CDC guidelines, opioid pain relievers be treated as highly addictive, controlled substances *not typically indicated for long-term use for chronic pain* outside of active cancer treatment, palliative care, and end-of-life care; and for which lobbying and marketing are inappropriate.”<sup>1201</sup>
- n. The 2017 VA/DoD guideline is even more emphatic, stating, “We recommend *against* initiation of long-term opioid therapy for chronic pain. (Strong against).”<sup>1202</sup> The authors stress that “Based on the evidence, it was considered that *opioid therapy should no longer be given when all nonopioid approaches fail due to the substantial risk of harms*. The [2016] CDC guideline states, ‘Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patients.’ Our guideline takes a *stronger stance against opioid therapy*, largely driven by the risk for development of opioid use disorder. Both guidelines find little evidence of benefit for long-term opioid use.”<sup>1203</sup> In 2022, the VA/DoD guideline was updated and strengthened: “Compared with the 2017 recommendation against the initiation of *long-term* opioid therapy, the updated recommendation against opioid therapy in general for chronic pain is broader and reflects the evidence that opioid therapy for any duration may be harmful.”<sup>1204</sup>
- o. I have reviewed a letter submitted by the American Medical Association to the CDC on June 16, 2020, advocating major revisions to the CDC 2016 Guidelines for opioid use.<sup>1205</sup> While this letter asserts that some patients are benefitting from long-term opioid therapy for chronic pain, it provides no data to support that assertion, nor to rebut the great weight of authority cited above. Further, the letter omitted the undisputed body of evidence of OUD and mortality, which would be exacerbated by the absence of the CDC and VA/DoD guidelines to limit dose and duration of opioid therapy. I agree with the AMA letter’s advocacy for a preference for non-pharmacologic and non-opioid therapies; however, the evidence supports the VA/DoD determination

<sup>1200</sup> Manchikanti, “ASIPP Guidelines”, fn. 415, above, at p. S10.

<sup>1201</sup> ASPPH Report, “Bringing Science”, fn. 24, above, at p. 11 (emphasis added).

<sup>1202</sup> Rosenberg JM, *et al.* Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines. *Pain Medicine*. 2018;19:928-941, at p. 930 (emphasis added).

<sup>1203</sup> *Id.* (emphasis added)

<sup>1204</sup> Sandbrink, “The Use of Opioids in the Management of Chronic Pain”, fn. 1180, above, at p.389. (emphasis in original)

<sup>1205</sup> James L. Madara, MD (AMA) to Deborah Dowell, MD (CDC), Re: Docket No. CDC-2020-0029, June 16, 2020, <https://searchlf.ama-assn.org/undefined/documentDownload?uri=%2Funstructured%2Fbinary%2Fletter%2FLETTERS%2F2020-6-16-Letter-to-Dowell-re-Opioid-Rx-Guideline.pdf>.

that opioids should no longer be given even when other approaches fail, due to the substantial risk of harms. Physicians' freedom to treat their patients as they choose is not absolute, but must be tempered by evidence and data. AMA's emphasis on physicians' freedom is out of proportion to the clear evidence of risk, and the lack of evidence of benefit, for long-term opioid therapy for chronic pain.

- p. On November 4, 2022, the Centers for Disease Control (CDC) issued the CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 (2022 Clinical Practice Guideline), which expanded and updated the 2016 CDC Opioid Prescribing Guideline.<sup>1206</sup> Earlier on February 9, 2022, the CDC issued and invited input on a draft clinical practice guideline.<sup>1207</sup> The 2022 Clinical Practice Guideline was the result of revisions to the draft clinical practice guideline, incorporating feedback from reviews by an independent federal advisory committee, peer reviewers, and the public.<sup>1208</sup> The revision was intended, in part, to address concerns that the 2016 CDC Guideline had been misinterpreted to set rigid limits on opioid dose and duration. Such limits could be particularly harmful to patients who had become physically dependent on high dose prescription opioids if their high dose opioids were abruptly tapered or discontinued. The potentially severe effects of opioid withdrawal are well-known, and such effects have been documented among patients who have been “cut off” from opioids by their prescribing doctors following issuance of the 2016 CDC Guidelines. Despite these revisions, the lead author of the Guideline, Deborah Dowell, MD, asserts that the 2022 Clinical Practice Guideline “retains the 2016 principles for prescribing opioids for chronic pain, including that clinicians should maximize use of nonopioid therapies and consider initiating opioid therapy only if the expected benefits for pain and function are anticipated to outweigh the risks and that when opioids are needed, clinicians should initiate therapy at the lowest effective dosage, carefully evaluate individual benefits and risks when considering increasing dosages, and avoid increasing the dosage above levels likely to yield diminishing returns in benefits relative to risks.”<sup>1209</sup>
- i. A key change in the 2022 Clinical Practice Guideline is the recommendation that clinicians “should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns

<sup>1206</sup> Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep* 2022;71(No. RR-3):1–95. DOI: <http://dx.doi.org/10.15585/mmwr.rr7103a1>

<sup>1207</sup> Centers for Disease Control and Prevention, CDC Clinical Practice Guideline for Prescribing Opioids – United States, 2022. (Feb. 9, 2022) <https://www.regulations.gov/document/CDC-2022-0024-0002>

<sup>1208</sup> Dowell, “CDC Clinical Practice Guideline - 2022”, fn. 1206, above.

<sup>1209</sup> Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. Prescribing Opioids for Pain - The New CDC Clinical Practice Guideline. *N Engl J Med*. 2022;387(22):2011-2013. doi:10.1056/NEJMp2211040, at p.2012.

in benefits relative to risks to patients,”<sup>1210</sup> replacing the previous recommendation that clinicians “should carefully reassess evidence of individual benefits and risks when considering increasing dosage to 50 morphine milligram equivalents (MME) or more per day, and should avoid increasing dosage to 90 MME or more per day...”<sup>1211</sup> The 2022 Clinical Practice Guideline still relies on the same evidence that supported the MME thresholds. The decision to leave specific MME thresholds out of the revised 2022 Guidelines was not unanimously supported by the members of the federal expert advisory committee, but the MME thresholds were ultimately left out, not because they’re inaccurate, but because the revised Guideline authors feared misapplication. Dowell noted, some expert advisers “felt strongly that clinicians needed [language citing specific opioid dosages and durations] and that it should not be omitted, but to discourage misapplication of thresholds the authors decided to “emphasize general principles” instead.<sup>1212</sup>

- ii. The 2022 Clinical Practice Guideline also incorporated new evidence regarding the validated effectiveness of nonopioid therapies.<sup>1213</sup> It now recommends that “Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient,” while noting that “Nonopioid therapies are at least as effective as opioids for many common types of acute pain.”<sup>1214</sup> It still also recommends that “Nonopioid therapies are preferred for subacute and chronic pain.”<sup>1215</sup> The Guidelines cite the 2018 Krebs SPACE trial<sup>1216</sup> as support<sup>1217</sup> and describe it as a “seminal randomized clinical trial.”<sup>1218</sup>
- iii. The CDC was targeted with significant lobbying efforts to replace the 50 MME and 90 MME dosage guidelines with a “physician’s judgment” standard, including by the American Medical Association, despite even stronger evidence of lack of benefit over non-opioids than existed in 2016. (Similar pressures were brought to bear on the HHS Task Force Report of 2019, which was inundated with public comments

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<sup>1210</sup> Dowell, “CDC Clinical Practice Guideline - 2022”, fn. 1206, above at p. 30.

<sup>1211</sup> Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645, at p. 1637.

<sup>1212</sup> Dowell, “Prescribing Opioids for Pain”, fn. 1209, above at p. 2013.

<sup>1213</sup> *Id.*, at p. 2012.

<sup>1214</sup> Dowell, “CDC Clinical Practice Guideline - 2022”, fn. 1206, above at p. 17.

<sup>1215</sup> *Id.*, at p. 21.

<sup>1216</sup> Krebs “Effect of opioid vs nonopioid medications”, fn. 1181, above. See additional discussion of Krebs (2018) at §C.7.g, above.

<sup>1217</sup> Dowell, “CDC Clinical Practice Guideline - 2022”, fn. 1206, above, at p. 23.

<sup>1218</sup> *Id.*, at p. 4.

from advocacy groups such as the U.S. Pain Foundation, which receives its funding from opioid manufacturers.)

- iv. In my opinion, the 2022 revised CDC Clinical Practice Guideline for Prescribing Opioids for Pain is the CDC's attempt to "thread the needle" between the scientific evidence, on the one hand, and the interests of those lobbying to remove specific dosage and duration guidelines on the other. Of note, while the 2016 Guideline states that physicians should use caution when increasing dosages above 50 MME per day, with a heightened caution and need to carefully justify increasing doses above 90 MME per day, the revised Guideline suggests caution when *any* increase in dose is contemplated.<sup>1219</sup>
- q. Opioids have been generally considered appropriate for cancer pain, because cancer treatment has been closely aligned with end-of-life care, a stage when risks of addiction are considered less important than potential palliative care. However, patients with cancer related pain, even at the end of life, are not immune to addiction and they should be monitored carefully for addiction and other adverse consequences, and should receive the lowest dose for the shortest possible duration.
  - i. A first-person perspective piece in the *New England Journal of Medicine*, describes the experience of an oncologist (cancer doctor) whose patient gets addicted to opioids.<sup>1220</sup> In my clinical experience, opioid misuse and addiction are as common among cancer patients as non-cancer patients.
  - ii. There were more than 15 million cancer survivors in the United States in 2016.<sup>1221</sup> Even patients with cancers once considered incurable, now go into remission for decades and more, emphasizing the need for caution in treating a very large population of patients with opioids.
- r. Opioids have been generally considered appropriate for short-term use in acute pain, pain lasting 12 weeks or less. However, a recent placebo-controlled trial comparing opioids to placebo in the treatment of acute non-specific low back or neck pain found no difference in efficacy on pain severity at 6 weeks. At one year, study results significantly favored placebo over opioids, while those

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<sup>1219</sup> 2022 Draft CDC Guidelines, fn, 1207, above, at p. 100. ("Clinicians should generally avoid unnecessary dosage increases, use caution when increasing opioid dosages, and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage.")

<sup>1220</sup> Loren AW. Harder to Treat Than Leukemia - Opioid Use Disorder in Survivors of Cancer. *N Engl J Med*. 2018;379(26).

<sup>1221</sup> Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev*. 2016. doi:10.1158/1055-9965.EPI-16-0133, at p. 1029.



in the opioid group experienced higher likelihood of medication misuse (20% vs 10% in the placebo group). The authors write, “Our findings show that even judicious, short-term use of an opioid conferred no benefits in pain reduction and led to a small increase in pain at the medium-term and long-term compared with placebo.”<sup>1222</sup>

**8. The Pharmaceutical Opioid Industry misrepresented that the risk of addiction to prescription opioids is “rare,” or “less than 1%,” when in fact prescription opioids are as addictive as heroin, and the risk of addiction is far higher than stated by the Industry. The best, conservative data show an opioid addiction prevalence of 10-30% among chronic pain patients prescribed opioids.**

- a. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.<sup>1223</sup> The addictiveness of prescription opioids has been demonstrated in many studies, yet the Pharmaceutical Opioid Industry has consistently downplayed this risk.
- b. A 2015 systematic review by Vowles, *et al.*, provides the most reliable pooled estimate of the risk of addiction (10-30%) in patients receiving chronic opioid therapy.<sup>1224</sup> The Vowles article has been cited by both the National Institute on Drug Abuse (NIDA) and the ASPPH Task Force, to state the risk of addiction and misuse of prescription opioids,<sup>1225</sup> reinforcing my opinion as to the validity of the Vowles review.
  - i. Vowles’ data synthesis prioritized studies using real world data designed to research opioid misuse and addiction. They also prioritized subjects from real world populations, rather than pre-screened clinical trial subjects enrolled in studies not designed to assess misuse or addiction. The authors adopted *a priori* criteria to assess study quality, and then checked their pooled results against the data from the highest quality studies.<sup>1226</sup> (By contrast, Fishbain *et al.*, described below, completely excluded studies that did not meet their quality standards,

<sup>1222</sup> Jones CMP, *et al.* Opioid analgesia for acute low back pain and neck pain (the OPAL trial): A randomized placebo-controlled trial. *Lancet*. 2023;1-9, at p. 8.

<sup>1223</sup> See, *e.g.*, Okie S, A flood of opioids, a rising tide of deaths. *NEJM* 2010;363(21): 1981-1985: Prescription opioids are “essentially legal heroin.” (Quoting FDA Advisory Committee member Lewis Nelson. “We need to think about how we would conduct a REMS [Risk Evaluation and Mitigation Strategy] if we were going to be marketing heroin.” at p. 1981.)

<sup>1224</sup> Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, Van Der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*. 2015. doi:10.1097/01.j.pain.0000460357.. at p. 569. I address the link between prescription opioid addiction and heroin addiction below in §C.9.

<sup>1225</sup> National Institute on Drug Abuse. *Opioid Overdose Crisis*. <https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis> (March 11, 2021); ASPPH Report, “Bringing Science”, fn. 24, above, at p. 14.

<sup>1226</sup> Vowles, “Rates of Opioid Misuse”, fn. 1224, above, at p. 570-571.

which they admitted were arbitrary.) Further, Vowles, *et al.* disclosed that they had no conflicts of interest.<sup>1227</sup> Because most available studies used patient questionnaires rather than objective urine drug screening, Vowles' analysis would represent a likely underestimate of addiction, despite a more appropriate selection of real world populations for the study.

- ii. In their systematic review and meta-analysis from 38 studies, Vowles, *et al.* cite a wide range of problematic prescription opioid use in patients being treated for a medical condition, ranging from <1% to 81% across studies. Across most calculations, rates of opioid misuse averaged between 21% and 29% (range, 95% confidence interval [CI]: 13%-38%), and rates of opioid addiction averaged between 8% and 12% (range, 95% CI: 3%-17%).<sup>1228</sup>
- iii. Even the lower risk classification of 8-12% would be considered a "very common" risk according to the World Health Organization and the Council of International Organizations of Medical Sciences:<sup>1229</sup>
  - A. Very common  $\geq 1/10$
  - B. Common  $\geq 1/100$  and  $< 1/10$
  - C. Uncommon  $\geq 1/1000$  and  $< 1/100$
  - D. Rare  $\geq 1/10,000$  and  $< 1/1,000$
  - E. Very rare  $< 1/10,000$
  - F. Although the US has not adopted a standard hierarchy like WHO/CIOMS, frequency of adverse events in product information material in the United States is consistent with the WHO standards: "rare" in US labels is commonly  $< 1/1000$ ; "Infrequent" is  $> 1/1,000$  to  $< 1/100$ ; and anything over  $1/100$  is "frequent."<sup>1230</sup>

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<sup>1227</sup> *Id.* at p. 575.

<sup>1228</sup> *Id.* at, pp. 572-573. It is noteworthy that well-respected scientific sources have cited Vowles' article as a reliable estimate of risk. *See also*, Els, *et al.*, High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2017 Oct; 2017(10): CD012299, citing the Vowles article as support for rates of addiction averaging between 8% and 12%.

<sup>1229</sup> World Health Organization, CIOMS,

[http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/trainingcourses/definitions.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf), at p. 10.

<sup>1230</sup> Eriksson R, Aagaard L, Jensen LJ, *et al.* Discrepancies in listed adverse drug reactions in pharmaceutical product information supplied by the regulatory authorities in Denmark and the USA. *Pharmacol Res Perspect.* 2014;2(3):1-10. doi:10.1002/prp2.38, at p. 6.

- iv. Vowles' definition of "misuse" as culled from the included articles is consistent with the DSM-5 definition of mild opioid use disorder.<sup>1231</sup> As such, the prevalence of opioid use disorder in Vowles' review using DSM-5 criteria is between 21-29%, including the spectrum from mild through severe OUD.<sup>1232</sup> (This is reasonably consistent with the Boscarino, *et al.* study<sup>1233</sup> described below.)
- v. As with other meta-analyses, reports of misuse/addiction were higher in studies which relied on urine drug testing instead of self-report. For example, included in the Vowles analysis, a study by Brown, *et al.* demonstrated the lower rates based on self-report versus those based on urine toxicology.<sup>1234</sup>
  - A. This was a nonrandomized, open-label study of morphine sulfate ER (Avinza) for a titration period of 2-4 weeks followed by treatment for 12 weeks, administered to patients in primary care settings, evaluated for risk stratification and aberrant behaviors (including urine screening, early renewal requests, increased dose without authorization, oversedation).<sup>1235</sup>
  - B. Only 561 (38%) of the 1,570 originally enrolled patients completed the study, despite its relatively brief duration of 12 weeks of treatment. Of the 890 patients for whom reasons for withdrawal were provided, 410 (46%) included adverse events or failure of treatment among their reasons to withdraw. Five percent were asked to withdraw due to investigator assessment of "high risk level for drug abuse/misuse" after enrollment, and another 5% for "noncompliance."<sup>1236</sup>

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<sup>1231</sup> Vowles, "Rates of Opioid Misuse", fn. 1224, above, at p. 574. Note that the Vowles article includes a basic definition of "Misuse: Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects." (at p. 570) However, Vowles also notes, "Several types of misuse were identified within studies and included underuse, erratic or disorganized use, inappropriate use (e.g., to manage symptoms of anxiety or other sorts of distress), use in conjunction with alcohol or illegal substances (e.g., marijuana), and, of course, overuse." (at p. 574).

<sup>1232</sup> *Id.* at p. 569.

<sup>1233</sup> Boscarino J, Rukstalis MR, Hoffman SN, *et al.* Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194. doi:10.1080/10550887.2011.581961.

<sup>1234</sup> Brown J, Setnik B, Lee K, *et al.* Assessment, stratification, and monitoring of the risk for prescription opioid misuse and abuse in the primary care setting. *J. Opioid Management.* 2011;(December):467-483 doi:10.5055/jom.2011.0088.

<sup>1235</sup> *Id.* at p. 468.

<sup>1236</sup> *Id.* at p. 473.

- C. The Vowles analysis incorporates the Brown study's assertion that 2-3% of patients exhibited aberrant drug-related behaviors during visits 2 through 4, and 6% at visit 5, listing those percentages in the "misuse" column.<sup>1237</sup>
- D. However, Urine Drug Screening (UDS) showed much higher rates of misuse and/or addictive use (although Vowles did not include these findings in the analysis): In particular, 17, 11, 11 and 15 subjects had positive UDS for oxycodone in weeks 2-5, despite prohibition of that drug after Visit 1.<sup>1238</sup> By week 5, there were 79 subjects remaining in the study, and the 15 subjects with positive UDS for oxycodone yield a rate of 19% misuse and/or addictive use. This finding provides objective evidence that the prevalence of aberrant drug-related behavior was approximately 3 to 9 times the "2-6%" rate of aberrant drug related behaviors reported by the investigators<sup>1239</sup> and cited by Vowles. Such use occurred despite patients having signed agreements to refrain from illicit drug use, and despite knowledge that UDS would be conducted.<sup>1240</sup>
- E. Objective measures of addictive/aberrant behavior like drug screening results are more reliable than questionnaire responses, and these data from the Brown study support that view.
- F. This study was Pfizer-sponsored. Authors included Pfizer/subsidiaries/consultants.<sup>1241</sup>
- vi. Also included in the Vowles analysis was a study by Fleming, *et al.*, again highlighting the discrepancy between self-report and urine toxicology.<sup>1242</sup>
  - A. This Fleming article reported on substance use disorders among 801 chronic pain patients receiving daily opioid therapy from the same Wisconsin primary care practices that provided the population analyzed in the Fleming article discussed above. Fleming reported a point prevalence of 3.8% for opioid use disorder and 9.7% for substance abuse and/or dependence,

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<sup>1237</sup> *Id.* at p. 572.

<sup>1238</sup> *Id.* at p. 475, Figure 2.

<sup>1239</sup> *Id.* at p. 476.

<sup>1240</sup> *Id.* at pp. 478-479.

<sup>1241</sup> *Id.* at p. 481.

<sup>1242</sup> Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance Use Disorders in a Primary Care Sample Receiving Daily Opioid Therapy. *J Pain*. 2007. doi:10.1016/j.jpaa.2012.02.008, at p. 579.

using DSM-4 criteria<sup>1243</sup> and Vowles incorporated these percentages into the data synthesis.

- B. The diagnoses included in the percentages above were based on a 2-hour interview of each patient by the doctor or nurse at the primary care practice.<sup>1244</sup> As referenced above, Fleming noted the large disparity between the patients' self-reporting of other drug use and the results of urine drug screening. There were 156 positive urine screens for cannabis compared to 106 self-reports, and 60 positive urine screens for cocaine compared to 24 self-reports.<sup>1245</sup>
- C. Although the article provided urine drug screen data on certain illicit drugs, sufficient to show the discrepancy between deceptive self-report and objective toxicology, the article did not provide data on the results of urine screens specifically for opioids, so there were no data to determine how many patients used opioids that were not prescribed (evidence of misuse), or less/no evidence of the prescribed opioids (evidence of possible diversion).
- D. Fleming also reported that "the frequency of opioid use disorders was 4 times higher in patients receiving opioid therapy compared with general population samples (3.8% vs 0.9%)."<sup>1246</sup>
- E. Despite acknowledging the disparity between toxicology tests and diagnoses based on interview data, Fleming concluded that the "3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering. The data presented in this paper support the use of opioids for the treatment of chronic pain by primary care physicians."<sup>1247</sup> I disagree with this interpretation of the findings, especially in light of (a) the acknowledged disparity between the urine drug screen rate and the rate based on self-reports; (b) the unreliability of the latter; and (c) the unwarranted assumption that opioid therapy would alleviate chronic pain and suffering as a trade-off for accepting the risk of dependence or addiction.

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<sup>1243</sup> *Id.* at p. 573.

<sup>1244</sup> *Id.* at p. 574.

<sup>1245</sup> *Id.* at p. 579.

<sup>1246</sup> Fleming, *et al.*, "Substance Use Disorders," fn. 1242, above, at p. 573.

<sup>1247</sup> *Id.* at p. 581.

- c. A study indicating a high risk of addiction from prescription opioids was published by Boscarino, *et al.*, who analyzed addiction rates in a large population of patients receiving opioids to treat a medical condition, and found a 41.3% lifetime prevalence of opioid use disorder (using DSM-5 criteria).<sup>1248</sup> The research in this study is strengthened by the fact that it was based on a random sample of outpatients seen in a large multispecialty group practice. Subjects were identified through drug orders in the electronic health records and subsequently were interviewed using the final DSM-5 criteria. Weaknesses include the low numbers willing to be interviewed (33%).<sup>1249</sup>
- i. “Using electronic records from a large US health care system, we identified outpatients receiving five or more prescription orders for opioid therapy in the past 12 months for noncancer pain (mean prescription orders =10.72; standard deviation =4.96). In 2008, we completed diagnostic interviews with 705 of these patients using the DSM-4 criteria. In the current study, we reassessed these results using the final DSM-5 criteria. Results: The lifetime prevalence of DSM-5 opioid-use disorders using the final DSM-5 criteria was 58.7% for no or few symptoms (<2), 28.1% for mild symptoms (2–3), 9.7% for moderate symptoms (4–5), and 3.5% for severe symptoms (six or more). Thus, the lifetime prevalence of “any” prescription opioid-use disorder in this cohort was 41.3% (95% confidence interval [CI] =37.6–45.0).”<sup>1250</sup>
- ii. “A comparison to the DSM-4 criteria indicated that the majority of patients with lifetime DSM-4 opioid dependence were now classified as having mild opioid-use disorder, based on the DSM-5 criteria (53.6%; 95% CI =44.1–62.8). In ordinal logistic regression predicting no/few, mild, moderate, and severe opioid-use disorder, the best predictors were age 65 years, current pain impairment, trouble sleeping, suicidal thoughts, anxiety disorders, illicit drug use, and history of substance abuse treatment.”<sup>1251</sup>
- iii. In my opinion, the moderate-severe categories of DSM-5 OUD are consistent with Vowles’ definitions of addiction, and the milder DSM-5 diagnoses are more consistent with Vowles’ definition of misuse.<sup>1252</sup> Accordingly, the totals of 13% “moderate to severe opioid use disorder” in Boscarino are consistent with Vowles’ findings of 8-12% “addicted”; further, Vowles’ finding of 21-29% “misuse” is reasonably consistent with Boscarino’s report of 28% with “mild opioid use

<sup>1248</sup> Boscarino J, Hoffman S, Han J. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Subst. Abuse Rehabil.* 2015;83. doi:10.2147/SAR.S85667, at p. 83.

<sup>1249</sup> *Id.* at p. 84.

<sup>1250</sup> *Id.* at p. 83.

<sup>1251</sup> *Id.*

<sup>1252</sup> Vowles, “Rates of Opioid Misuse”, fn. 1224, above, at p. 574.



disorder.” In other words, both of these publications are reasonably consistent in assessing the risk of opioid addiction, ranging from mild to severe, in a clinical population of patients receiving opioids.

- d. Even very limited exposure to prescription opioids can result in addiction, as evidenced by a study in teens and young adults: 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that 6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%. This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.<sup>1253</sup>
- e. A 2019 study found that for opioid-naïve individuals receiving an initial opioid prescription between 2011-2014, “long-term opioid use (3+ months) is associated with more than double the risk of incident OUD and opioid-related death.”<sup>1254</sup> In fact, the cumulative incidence of opioid use disorder rose for each time period measured after opioid naïve individuals received an opioid prescription, so that for those receiving an initial opioid prescription in 2011, the cumulative incidence of OUD was 0.62% at 6 months, 1.18% at 1 year, 2.244% at 2 years, 3.79% at 3 years and 4.90% at 4 years.<sup>1255</sup>
- f. Numerous other publications have reported addiction rates from prescription opioids higher than those that appear in the Pharmaceutical Opioid Industry promotional materials that I have reviewed. These include the following prevalence studies cited in the Vowles<sup>1256</sup> data synthesis: Manchikanti (2003),<sup>1257</sup> Cowan (2003),<sup>1258</sup> Adams (2006),<sup>1259</sup> Fleming (2007),<sup>1260</sup> Banta-

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<sup>1253</sup> Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. *JAMA Intern Med.* 2018, at p. E6.

<sup>1254</sup> Burke LG, *et al.* Trends in opioid use disorder and overdose among opioid-naïve individuals receiving an opioid prescription in Massachusetts from 2011 to 2014. *Addiction.* 2019:1-12, at p. 9

<sup>1255</sup> *Id.*, p. 6, Table 3

<sup>1256</sup> Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 1224, above.

<sup>1257</sup> Manchikanti, *et al.* Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *J Ky Med Assoc* 2003;101:511–17, at p. 511.

<sup>1258</sup> Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG. A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med.* 2003;4(4):340-351, at p. 340.

<sup>1259</sup> Adams EH, Breiner S, Cicero TJ, *et al.* A Comparison of the Abuse Liability of Tramadol, NSAIDs, and Hydrocodone in Patients with Chronic Pain. *J Pain Symptom Manage.* 2006;31(5):465-476, at p. 465.

<sup>1260</sup> Fleming, *et al.*, “Substance Use Disorders,” fn.1242, above, at p. 573.

Green (2009),<sup>1261</sup> Schneider (2009),<sup>1262</sup> Edlund (2007),<sup>1263</sup> Højsted (2010),<sup>1264</sup> Jamison (2010),<sup>1265</sup> Passik (2011),<sup>1266</sup> and Meltzer (2012),<sup>1267</sup> which reported addiction at 8.4%, 2.8%, 4.9%, 3.8%, 13%, 15.7%, 0.7%, 14.4-19.3%, 34.1%, 6-11%, and 23%, respectively. With one exception, all of these studies showed addiction prevalence multiple times higher than the “less than one percent” figure that Defendants continued to cite, while omitting data from these peer-reviewed studies of relevant, real world populations of chronic opioid patients.<sup>1268</sup>

- g. The above-described studies show that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants before and throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was “less than 1%,” or “rare,” or “uncommon,” and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy. Internal documents show that Defendants were aware of the link between prescription opioids and opioid misuse, diversion, addiction and death, as discussed below.

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<sup>1261</sup> Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn D a. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug Alcohol Depend.* 2009;104(1-2):34-42, at p. 37.

<sup>1262</sup> Schneider, MD, PhD JP, Kirsh, PhD KL. Defining clinical issues around tolerance, hyperalgesia, and addiction: A quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. *J Opioid Manag.* 2010;6(6):385-395, at p. 390.

<sup>1263</sup> Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? *Pain Med.* 2007. doi:10.1111/j.1526-4637.2006.00200.x, at p. 651.

<sup>1264</sup> Højsted J, Nielsen PR, Guldstrand SK, Frich L, Sjøgren P. Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain.* 2010;14(10):1014-1020, at p. 1014.

<sup>1265</sup> Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender Differences in Risk Factors for Aberrant Prescription Opioid Use. *J Pain.* 2010. doi:10.1016/j.jpain.2009.07.016, at p. 5.

<sup>1266</sup> Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. *J Pain Symptom Manage.* 2011;41(1):116-125, at p. 116.

<sup>1267</sup> Meltzer, E, Rybin, D, *et al.* Aberrant Drug-Related Behaviors: Unsystematic Documentation Does Not Identify Prescription Drug Use Disorder. *Pain Med.* 2012 November; 13(11): 1436-1443, at p. 1437.

<sup>1268</sup> The sole exception, the Edlund (2007) study, can be explained in that the 0.7% incidence pertained to the entire healthcare database, rather than the subset of prescription opioid users. As to the latter group, the incidence of addiction was actually 7.3%, which is consistent with the other data synthesized by Vowles. Edlund MJ, *et al.*, Do Users of Regularly Prescribed Opioids Have Higher Rates of Substance Use Problems Than Nonusers? *Pain Medicine.* 2007; 8(8):647-656, at p. 651. I have reviewed the Report of Dr. Katherine Keyes, which includes the basis for correction of Vowles' misinterpretation of the Edlund study and corrects the overall prevalence of addiction based on the corrected data; I have also reviewed correspondence from the journal indicating that Dr. Keyes' re-analysis of the Vowles study has been accepted for publication. Further, Edlund acknowledged, “Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates.” *Id.* at p. 654. Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

- i. On April 22, 2011, Joseph Tomkiewicz, Corporate Investigator at AmerisourceBergen, sent an email to colleagues under the subject “Saw This and Had To Share It ...”<sup>1269</sup> It was a parody written to the tune of the Beverly Hillbillies: “Come and listen to a story about a man named Jed, A poor mountaineer, barely kept his habit fed.... Said Sunny Florida is the place you ought to be, So they loaded up the truck and drove speedily, South, that is, Pain Clinics, cash ‘n carry, A Bevy of Pillbillies .... Pill Mills that is. Buy some pills. Take a load home.”<sup>1270</sup> This is shocking for its gross disregard of human suffering caused by the opioid epidemic. Just as shocking is the fact that the offensive email was circulated among several high-ranking regulatory affairs executives and diversion control investigators at Amerisource Bergen, who not only failed to express disapproval, but rather stated, “I sent this to you a month or so ago--nice to see it recirculated,” with a “smiley face” icon.<sup>1271</sup>
- ii. On July 2, 2012, the same AmerisourceBergen employee, Joseph Tomkiewicz, also sent to colleagues under the subject “Oxycontin for kids”, an image resembling a Kellogg’s cereal box, but instead of “Kellogg’s” it reads “Killogg’s”, the cereal is called “SMACK”, a slang term for heroin, and the cereal box features a frog with a syringe getting ready to inject, holding up a spoonful of pills, next to a bowl of coupons labeled “Free Trial Offer” as shown below:<sup>1272</sup>

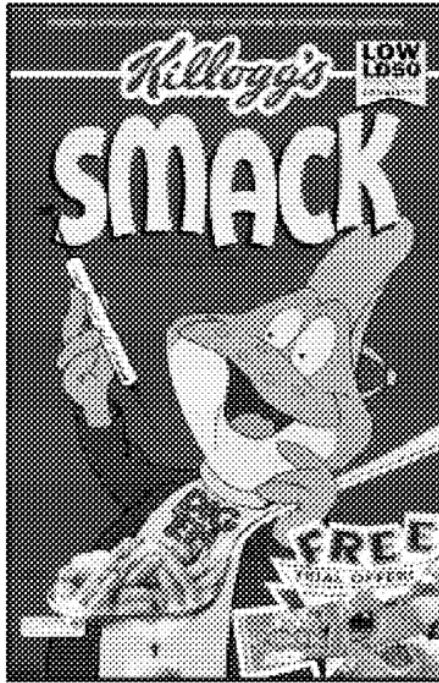
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<sup>1269</sup> ABDCMDL05795672

<sup>1270</sup> *Id.*

<sup>1271</sup> *Id.* The email’s recipients included Julie Eddy (Director State Government Affairs) Chris Zimmerman (Vice President Corporate Security and Regulatory Affairs), Edward Hazewski (Director Diversion Control Program) , Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Paul Ross (Senior Director Corporate Security Regulatory Affairs), Bruce Gundy (Director of Investigations) , Robert Crow (Director Security Services), and Steve Mays (Senior Director Corporate Security and Regulatory Affairs - Group Compliance Officer, Drug Distribution). *See* <https://www.linkedin.com/in/julie-eddy-458b118>, <https://www.linkedin.com/in/chriszimmerman>, <https://www.linkedin.com/in/edwardhazewski>, <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, ABDCMDL05775790, <https://www.linkedin.com/in/bruce-gundy-5b5085a>, <https://www.linkedin.com/in/robert-crow-7b97aa192>, <https://www.linkedin.com/in/steve-mays-47833336>.

<sup>1272</sup> ABDCMDL00532594



- iii. This image encapsulates the link between prescription opioids, industry promotion of those opioids through marketing strategies like coupons for free samples, and the development of opioid addiction which in some cases leads to illicit opioids like heroin. As in the case of the “Pillbillies” email, the “Smack” email was circulated among several employees without evidence of any objections.<sup>1273</sup>
- iv. On June 19, 2015, a memorandum from Healthcare Distribution Management Association (HDMA) titled “Strategy to Turn the Tide in West Virginia,” summarizes suggestions for distributors to fend off negative press and lawsuits due to their role in inciting the opioid epidemic.<sup>1274</sup> This memorandum includes the statement, “The fact is that 200 million pills over a four-year period is a significant problem. The story is made worse given the following: The distributors do not want to make their sales data public.... While patient access issues can help support the need for distributors, they can also turn against distributors, as these companies must self-monitor and restrict the

<sup>1273</sup> *Id.* The email’s recipients included Kevin Kreutzer (Diversion Control Investigator), David Breitmayer (Diversion Control Investigator), Edward Hazewski (Director Diversion Control Program), and Elizabeth Garcia (Corporate Investigator). See <https://www.linkedin.com/in/kevin-kreutzer-b1763512>, <https://www.linkedin.com/in/davebreitmayer>, <https://www.linkedin.com/in/edwardhazewski>, ABDCMDL00532649.

<sup>1274</sup> ABDCMDL00269293

supply of medicine to protect their ability to continue serving the needs of doctors, pharmacists, and their patients.”<sup>1275</sup> HDMA is an alliance of pharmaceutical distributors, largely funded by the Defendants in this litigation.<sup>1276</sup>

- v. In a 2001 discussion regarding abuse reports relating to Duragesic, Janssen’s VP of Pain, Steve Zollo stated, “let’s be clear about this issue – As the use of Duragesic continues to rise (which it will), so will drug abusers trying to find creative ways to extract fentanyl from the patch. That’s why it’s a scheduled drug. As our use goes up, so will published reports of abuse.”<sup>1277</sup> Yet in a 2001 Duragesic patient guide, Janssen made false and misleading statements regarding the addictive potential of Duragesic, stating that “addiction is relatively rare when patients take opioids appropriately.”<sup>1278</sup>
- vi. In 2001, Janssen convened an advisory board to discuss the Duragesic patch. When the topic of Duragesic’s addictive potential was raised, advisory board members, who were all KOLs in the field of pain, had this to say:
  - A. “All opioids are in the same class and have the same potential for abuse.”<sup>1279</sup>
  - B. “So why is OxyContin so subject to abuse? ... Availability - \$1B worth on the market. Street price indicates likelihood of diversion.”<sup>1280</sup>
  - C. “Drug abusers will figure out how to abuse Duragesic once it is more available .... As market share goes up, so will abuse. Over-promising on the lack of abuseability is what got OxyContin in trouble. Duragesic should not repeat the same mistake.”<sup>1281</sup>
  - D. These comments make it clear that members of the advisory board were well aware of the risks of misuse, addiction, and overdose deaths caused by prescription opioids, and that these risks were directly tied to availability, which increases the risk of patients getting addicted, and also diversion to non-patients.

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<sup>1275</sup> *Id.*

<sup>1276</sup> Healthcare Distribution Alliance (formerly known as the HDMA) leadership remains with David Neu of AmerisourceBergen, <https://www.hda.org/persons/david-neu>

<sup>1277</sup> JAN-MS-00287030 at -7031.

<sup>1278</sup> JAN-MS-02757826 at -7847.

<sup>1279</sup> JAN-MS-00481055 at -1059.

<sup>1280</sup> *Id.*

<sup>1281</sup> *Id.* at 1060.

Despite the KOLs advice, Janssen promoted Duragesic in ways similar to those that “got OxyContin in trouble,”<sup>1282</sup> including free samples and aggressive marketing of purported low risk of addiction (*See* §C.4.e-f. and §6.c. for discussion of Duragesic free samples and promotion) .

- h. Opioid manufacturers have sought to counter evidence of addiction risk by claiming ‘abuse-deterrent’ status for their products. For example, Janssen sought FDA approval of an “abuse deterrence” claim for tapentadol (Nucynta). However, an FDA Memorandum in 2008 noted that tapentadol displayed “high abuse potential comparable to that of hydromorphone, a drug that is associated with high levels of abuse.”<sup>1283</sup> The FDA authors likened tapentadol to “other strong opioids such as hydromorphone and oxycodone,” and warned against using tapentadol IR “chronically as this increases the adverse event profile, including the likelihood of addiction and abuse.”<sup>1284</sup> Further, the memorandum noted that tapentadol causes dependence and subjective withdrawal on par with oxycodone.<sup>1285</sup>
- i. A study by Butler *et al.* in *Pain Medicine* (2015), sponsored by Janssen, reports on a population of about 114,000 patients evaluated for prevalence and prescription-adjusted prevalence of self-reported, past 30-day “abuse” of tapentadol in comparison to several other opioids, between January 2011 and September 2012.<sup>1286</sup> Tapentadol IR “abuse” prevalence was reported to be lower than all other opioids except fentanyl, while tapentadol ER “abuse” prevalence was reported to be lower than other opioids except hydromorphone.<sup>1287</sup> (Of interest, 20.8% of the population self-reported “abuse” of analgesics within the last 30 days.)<sup>1288</sup> Most importantly, rate of “abuse” adjusted for number of prescriptions<sup>1289</sup> (tapentadol had far fewer prescriptions than other opioids), demonstrates that tapentadol “abuse” was greater than tramadol and nearly identical to hydrocodone. It is likely that tapentadol, with a similar “abuse potential” to hydrocodone, would

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<sup>1282</sup> *Id.*

<sup>1283</sup> Food and Drug Administration Center for Drug Evaluation and Research (FDA-CDER), Application Number: 22-304 (November 4, 2008), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2008/022304s000\\_OtherR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_OtherR.pdf), at p. 2. The relatively lower rates of misuse and diversion of tapentadol formulations in the community to date are likely a function of lower prescribing rates, a shorter period since the drug was approved for sale, and lower level awareness of the drug among prescribers, patient consumers, and individuals with opioid addiction, not an intrinsically lower abuse potential of tapentadol.

<sup>1284</sup> *Id.* at p. 3.

<sup>1285</sup> *Id.* at p. 9.

<sup>1286</sup> Butler SF *et al.* Tapentadol Abuse Potential: a postmarketing evaluation using a sample of individuals evaluated for substance abuse treatment. *Pain Medicine*. 2015;16: 119-130, at p. 119.

<sup>1287</sup> *Id.*

<sup>1288</sup> *Id.* at p. 122.

<sup>1289</sup> *Id.* at p. 119.



show similar rates of addiction and diversion if prescribed at equal volumes.

- ii. A study by Cepeda *et al.* (2013), also Janssen-funded, reported a 65% lower rate of “abuse” in a relatively small cohort of 6,000 total tapentadol subjects compared to 37,000 oxycodone subjects, identified in 2010 and followed for one year.<sup>1290</sup> However, the study provided no details as to the duration of exposure to either drug. Since duration of exposure is a significant cause of opioid use disorder, the absence of such data weakens the validity of the findings. Also, there are significant differences in prescribing rates between tapentadol and oxycodone, with much higher prescribing for oxycodone. Comparing these two drugs fails to take into account the longer history on the market and greater drug awareness for oxycodone. This is further supported by the animal and human studies finding tapentadol comparable to morphine, hydromorphone, and oxycodone in its likeability, reinforcing properties, and propensity for physiologic dependence, as noted in the 2008 FDA memorandum referenced above.<sup>1291</sup>
- iii. For the same reasons, a drug diversion surveillance study by Dart *et al.*, which finds relatively low rates of tapentadol diversion, is not a good measure of problematic opioid use in the community.<sup>1292</sup> Lower rates of tapentadol diversion are likely attributable to lower tapentadol prescribing rates and the ready availability of other opioids in the community. This opinion is supported by FDA reviewers, who stated in a 2013 letter to Janssen that in regard to tapentadol “abuse” in the community, “it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper-resistant characteristics of the extended-release formulation.”<sup>1293</sup>
- i. Tramadol is an addictive opioid yet was marketed as a “non-narcotic.”
  - i. After ingestion, tramadol is metabolized by the cytochrome P450 2D6 liver enzyme into an active metabolite that binds the opioid receptors and exhibits the same properties as other opioids, like morphine. J&J was well aware of tramadol’s opioid status before marketing it to the

<sup>1290</sup> Cepeda, MS *et al.* Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *Journal of Pain*. 2013;14(10): 1227-1241 at p. 1227.

<sup>1291</sup> FDA-CDER, “22-304”. fn. 1283, above, at pp. 8-10.

<sup>1292</sup> Dart RC, *et al.* Assessment of the abuse of tapentadol immediate release: the first 24 months. *Journal of Opioid Management* 2012; 8:395-402.

<sup>1293</sup> FDA-CDER Letter to Janssen (August 1, 2003). JAN-MS-00704213 at -4219.

public and was specifically instructed not to market tramadol as non-scheduled, i.e. non-addictive, given its robust activity at the opioid receptor.<sup>1294</sup> Despite knowledge of tramadol's potent activity at the opioid receptor, and despite a direct warning from the FDA, as shown below J&J falsely marketed tramadol as “non-narcotic” and repeatedly called attention to its unscheduled status, thus misleading prescribers into thinking tramadol is safer than other opioids and carries less risk of addiction.

- ii. The 1995 tramadol New Drug Application (NDA) makes it clear that manufacturers knew from before tramadol was marketed that the mechanism of action is that of an opioid. The original labeling for ULTRAM (tramadol) stated, “ULTRAM’s opioid activity derives from low affinity binding of the parent compound to u-opioid receptors and higher affinity binding of the M-1 metabolite....,” and the NDA Review of Pharmacology Toxicology Data stated, “This metabolite [M1] appears to play a major role in the opioid binding and analgesic effects, 4 times to nearly 200 times as potent as the parent tramadol and is often present at equivalent blood levels.”<sup>1295</sup>
- iii. In a letter from the FDA to the manufacturers dated March 3, 1995, manufacturers were warned not to call attention to tramadol’s (Ultram’s) status as a non-scheduled, i.e. non-addictive drug: “As Ultram may have an abuse potential of an unknown degree, you are not permitted to advertise, promote or market the drug product by calling attention to its unscheduled status under the U.S. Controlled Substance Act.”<sup>1296</sup>
- iv. In a 2008 internal J&J document, under “Strengths (Prioritized)”, is the statement: “Ultram ER [tramadol extended release] is non-narcotic which mid-level practitioners can prescribe.”<sup>1297</sup> The reference to mid-level practitioners implies that tramadol is safer than “narcotics” *i.e.* opioids, and hence can be prescribed by nurse practitioners who have less training in the risks of pharmacotherapy.
- v. The “Ultram ER Core Visual Aid Tour” depicts tramadol (Ultram ER) as a safer stepping-stone in a “pain treatment ladder” between non-opioid medications like acetaminophen/NSAIDs and “scheduled narcotics.” See “Key Points – PAIN LADDER: Use ULTRAM ER before moving to scheduled narcotics to treat moderate chronic pain;

<sup>1294</sup> FDA-CDER. NDA 20-281 File. (March 3, 1995).

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/pre96/020281Orig1s000rev.pdf..](https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf..)

<sup>1295</sup> *Id.* at pp. 8, 332.

<sup>1296</sup> *Id.* at p. 5.

<sup>1297</sup> JAN-TX-00022608, produced natively at \*2.

Around the clock pain deserves around the clock treatment without the concerns of scheduled narcotics.”<sup>1298</sup> Although it is accurate that tramadol was not scheduled before 2014, this pain treatment ladder is misleading because it suggests that tramadol is not an opioid, and that tramadol is safer than opioids, neither of which is true.

- vi. Tramadol sales representatives were coached to say the following to prescribers while showing them pictures from a direct-to-consumer television ad for Ultram ER, of people looking healthy and happy while engaged in different physical activities - hiking, playing on the beach, climbing stairs: “Doctor, after seeing this commercial, your patients may come to you asking about treatment options, including those that work around the clock. Those patients with chronic low back or osteoarthritis pain may be especially interested. Let’s discuss such a challenging patient in your practice – maybe you have a 50 year old female with chronic OA pain who needs to treat her pain on a daily basis and isn’t getting sufficient pain relief from her prescription NSAIDs, but whom you would rather not move to a scheduled narcotic. For that patient, why not put her on ULTRAM ER before moving her to a scheduled narcotic?”<sup>1299</sup> (“Ultram ER Core Visual Aid Tour”) The suggestion here is that Ultram ER is somehow less risky than other opioids because it was not “scheduled.” There is no evidence to support this suggestion and substantial evidence to the contrary.
- vii. Tramadol is addictive, as demonstrated by the references below.
- viii. In recognition of its addictive potential, in 2014 tramadol was changed from a non-scheduled drug, to a scheduled drug (Schedule IV).<sup>1300</sup>
- ix. A study of treatment-seeking adolescents at a substance use treatment facility in Sweden showed “tramadol was by far the most prevalent opioid detected.”<sup>1301</sup>
- x. A study of long-term use of tramadol following acute exposure, published in the British Medical Journal (BMJ 2019,) states: “Our study suggests that tramadol carries a similar or somewhat greater risk of transitioning from acute to prolonged use compared with other short acting opioids. Although prescribing was relatively infrequent (4% of patients with opioid fills, including those who received tramadol with

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<sup>1298</sup> JAN-TX-00001492, produced natively at \*9.

<sup>1299</sup> *Id.* at \*7

<sup>1300</sup> Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. 79 Fed. Reg. 37,628 (July 2, 2014).at p. 37628

<sup>1301</sup> Olsson MO, *et al.* High rates of tramadol use among treatment-seeking adolescents in Malmo, Sweden: a study of hair analysis of nonmedical prescription opioid use. *Journal of Addiction* 2015:1-9, at p. 1.

other short acting opioids), tramadol was the third most frequently prescribed opioid in this study (after hydrocodone and short acting oxycodone), and its use seems to be increasing (fig 1).<sup>1302</sup> The authors conclude, “Our findings suggest that from the standpoint of risk of dependency, clinicians prescribing tramadol for acute pain should exercise a level of caution similar to that surrounding the prescribing of other short acting opioids, including those on higher Drug Enforcement Administration schedules.”<sup>1303</sup>

- A. Persistent medical use of opioids is a risk factor for addictive use. Short-term tramadol prescribing leads to persistent use, especially as doses increase. Thiels reported that receipt of tramadol alone was associated with a 6% increase in the risk of additional opioid use relative to other short-acting opioids; a 47% increase in the risk of persistent opioid use (defined as episodes of use lasting 90 or more days, that started in the 180 days following surgery); and a 41% increase in the most stringent category of persistent use (the CONSORT criteria; opioid use lasting at least 90 calendar days and including either 10 or more opioid fills or 120 or more days supply); all of these increases met criteria for statistical significance.<sup>1304</sup> Thiels also reported that doses of 300 MME and larger were associated with higher risk of prolonged use (odds ratios 1.1 to 1.6).<sup>1305</sup> This aligns with CDC data supporting the conclusion that the risk of prolonged use increases significantly when patients receive prescriptions for more opioids.<sup>1306</sup>
- B. A 2022 study found that 29.9% of patients transitioned from acute opioid use to chronic opioid use and risk factors for the transition from acute to chronic use included prescribing of Tramadol.<sup>1307</sup> The authors stated, “... our findings are aligned with recent reports that Tramadol may be a high-risk opioid for future abuse.”<sup>1308</sup>

<sup>1302</sup> Thiels CA, *et al.* Chronic use of tramadol after acute pain episode: cohort study. *BMJ* 2019;365: |1849, 1-10 at pp. 5-6.

<sup>1303</sup> *Id.* at p. 6.

<sup>1304</sup> *Id.* at p. 1.

<sup>1305</sup> *Id.*, at p. 6.

<sup>1306</sup> Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:265–269

<sup>1307</sup> Johnson DG, *et al.* Prescription quantity and duration predict progression from acute to chronic opioid use in opioid-naïve Medicaid patients. *PLOS Digit Health*. 2022;1(8):1-14, at p. 1.

<sup>1308</sup> Johnson, “Prescription quantity and duration”, fn. 1307, above, at p. 10.

- C. Tramadol manufacturers coached sales representatives to push higher doses: “Key Points: 100 mg is only starting dose for most patients – will likely need to go to 200 or 300 mg. Sample Detail: ‘So if we go back to that 50 year old female patient with chronic OA pain, for whom scheduled narcotics are inappropriate does it make sense to prescribe ULTRAM ER and use it on a daily basis to provide effective pain relief? Good. There are three strengths – 100, 200 and 300mg. For patients not already on tramadol, you want to start on 100mg, increasing the dose by 100mg increments every 5 days. The 100 mg dose is just a starting dose for most patients.’”<sup>1309</sup>
- xi. Lay press articles have detailed widespread tramadol misuse, addiction, and diversion abroad. For example, a 2015 article reported that tramadol was “ubiquitous” in Egypt, and a clinic physician stated that up to 40% of his patients were “addicted” to tramadol.<sup>1310</sup> Another tramadol article reported that “Fueled by cut-rate Indian exports and inaction by world narcotics regulators, tramadol dependency extends across Africa, the Middle East and into parts of Asia and eastern Europe.”<sup>1311</sup> The same article reported that, in the U.S., emergency room visits related to tramadol had tripled between 2005-2011, and that, in Northern Ireland, “tramadol is killing more people than heroin.”<sup>1312</sup> These sources provide additional support for the conclusion that tramadol is an addictive and dangerous drug.
- xii. The misleading message that tramadol is a “non-narcotic” penetrated the medical literature, including government reports and peer reviewed clinical studies, creating a false sense of safety about tramadol.
- A. In a September 2011 Government Accountability Office Report to Congressional Requesters on the problem of ‘doctor shopping’, tramadol is listed in Table 1 as a “non narcotic painkiller.”<sup>1313</sup>
- B. Yet within the report tramadol is among the most common drugs that patients engaged in ‘doctor shopping’ to obtain,

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<sup>1309</sup> JAN-TX-00001492, produced natively at \*12.

<sup>1310</sup> Drug Abuse in Egypt: A pill for work and play, The Economist, April 18, 2015.

<sup>1311</sup> Justin Scheck, Tramadol: The opioid crisis for the rest of the world, Wall St. J., Oct. 19, 2016.

<sup>1312</sup> *Id.*

<sup>1313</sup> US. Government Accountability Office. (2011, September). Medicare Part D: Instances of questionable access to prescription drugs, (Publication No. GAO-11-699.), at p. 11.

fifth behind hydrocodone, oxycodone, morphine, and fentanyl, in a list of fourteen highly addictive prescription drugs.<sup>1314</sup>

- C. J&J's own published studies included misleading claims based on tramadol's non-scheduled status. For example, a 2007 study by Ortho-McNeil Janssen employees stated, "Concerns about regulatory scrutiny can cause the underprescription of conventional opioids and subsequent unrelieved or undermanaged pain. Thus, tramadol may be an option to postpone the use of conventional opioids while providing effective pain relief."<sup>1315</sup> This statement is misleading in that it differentiates between tramadol and "conventional opioids," when in fact tramadol's mechanism of action includes the M1 metabolite that acts in the same manner as a "conventional opioid," and it promotes such use on the basis that "regulatory concerns" would thereby be avoided – a coded reference to the tramadol's non-scheduled status, which J&J had been instructed not to use in its promotion of the drug.<sup>1316</sup>

xiii. I personally experienced the marketing message that tramadol was not an opioid and was therefore safer and less addictive than opioid pain medications. It is my opinion that my experience was not unique, and that similar or identical messages were conveyed to the medical community in general. Tramadol prescribing went up between 2009 and 2017, even as prescribing of other opioids went down.<sup>1317</sup> With growing national awareness of the opioid epidemic, J&J promoted tramadol as a 'safer alternative', despite evidence of abuse, addiction, and risk of other serious side effects.

- A. As tramadol prescribing went up, so did reports of harm, including addiction and death, as described below.
- B. An independent Steering Committee tasked with monitoring tramadol after it went on the market found multiple reports of severe opioid withdrawal following tramadol (Ultram) cessation. Further, in some cases patients were exhibiting symptoms of withdrawal "not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion and unusual sensory experiences such as numbness and tingling in one or more extremities.

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<sup>1314</sup> *Id.* at Table 2, p. 12.

<sup>1315</sup> Vorsanger G, *et al.*, Post hoc analysis of a randomized, double-blind placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther* 2007; 29:2520-2535, at p. 2530.

<sup>1316</sup> FDA-CDER. NDA 20-281 File. (March 3, 1995).

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/pre96/020281Orig1s000rev.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf).

<sup>1317</sup> Thiels, "Chronic Use of Tramadol", fn. 1302, above, at Figure 1.



Withdrawal symptoms of either type were one of the more prevalent adverse events associated with chronic Ultram use, comprising nearly 40% of all adverse events reported with Ultram. Most of these consisted of typical opiate withdrawal symptoms, but 1 in 8 cases presented as atypical. These results indicate that physicians and other healthcare professionals need to be aware of the potential of Ultram to induce withdrawal of the classical opioid type, and that atypical withdrawal may also occur.”<sup>1318</sup>

- C. A study from the United Kingdom showed prevalence of tramadol users increased from 2000 to 2015, and then significantly reduced after tramadol was made a Schedule IV drug (2014). “Both annual tramadol utilization and rate of tramadol-related deaths increased before tramadol classification and decreased thereafter.”<sup>1319</sup>
- D. A 2010 study analyzed tramadol poisoning data from 2003-2009 in the States of West Virginia, Ohio, Kentucky and Arkansas. In 2007-08, Kentucky and Arkansas imposed Schedule IV status on tramadol (several years before the FDA acted to do so), while tramadol remained unscheduled in West Virginia and Ohio.<sup>1320</sup> The study showed that poisonings due to tramadol rose in West Virginia and Ohio throughout the study period, while tramadol poisonings rose in Kentucky and Arkansas only until Schedule IV status was imposed, and declined thereafter.<sup>1321</sup> This study period was contemporaneous with the publication of the Vorsanger article promoting the use of tramadol as an alternative to “scheduled” opioids.
- j. In addition to being falsely marketed as non-narcotic and safer/less addictive than other opioids, tramadol was also falsely marketed as safer than non-opioid pain medications like acetaminophen and ibuprofen.
- i. From Ultram ER Core Visual Aid Tour: “Sample Detail: ‘ULTRAM ER gives you added confidence due to its safety profile. As you know from your experience with tramadol, ULTRAM ER is not a scheduled

<sup>1318</sup> Senay EC, *et al.* Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence* 2003;69:233-241, at p. 233.

<sup>1319</sup> Chen T-C, *et al.* A 15-year overview of increasing tramadol utilization and associated mortality and the impact of tramadol classification in the United Kingdom. *Pharmacoepidemiol Drug Saf.* 2018;27:487-494, at p. 487.

<sup>1320</sup> Spiller HA, *et al.* Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. *Annals of Pharmacotherapy* 2010;44:1016-1021, at p 1017

<sup>1321</sup> *Id.* at pp. 1018, 1020.

product and is not associated with the GI or CV warnings of NSAIDs or COX-2s, and ULTRAM ER can be used safely for long term therapy. Please make sure you are familiar with this important Safety Information before you prescribe ULTRAM ER.”<sup>1322</sup>

- ii. Because of tramadol’s unique metabolism and mechanism of action, it poses additional risks that do not occur with standard non-opioid medications like acetaminophen and ibuprofen.
  - A. The enormous inter-individual variability in CYP2D6 metabolism means that tramadol imposes risks on some patients that are greater than the risks for others, because the degree of metabolism in a given individual is unpredictable and unknown prior to the patient’s experience of an adverse event. Poor metabolizers won’t get sufficient analgesic effects of tramadol, and thus can be left without pain relief. Rapid metabolizers will effectively get more opioids, making them more vulnerable to toxicity.<sup>1323</sup>
  - B. Case reports of pediatric patients with overactive CYP2D6 enzymes dying from tramadol have been reported. “These ultra-rapid metabolizers experience an increase in the production of active metabolites of codeine and tramadol, which can lead to oversedation, respiratory depression, and death.”<sup>1324</sup> As a result, in 2017, the U.S. Food and Drug Administration updated their warnings regarding tramadol use, making tramadol contraindicated in patients under 12 years of age.<sup>1325</sup>
  - C. Further, administering tramadol with other medications increases the unpredictability of its metabolism. “Comedication may compromise drug safety by increasing the risk of drug interactions and adverse events, a fact often underestimated in patients. Comedication can produce enzyme induction or inhibition mimicking genetic defects, which also contributes to the variable response to drugs.”<sup>1326</sup>

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<sup>1322</sup> JAN-TX-00001492, produced natively at \*10

<sup>1323</sup> Stamer UM, *et al.* Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology & Therapeutics* 2007;82(1):41-47.

<sup>1324</sup> Fortenberry M, *et al.* The use of codeine and tramadol in the pediatric populations – what is the verdict now? *J Pediatr Health Care* 2019;33:117-123, at p. 117

<sup>1325</sup> *Id.*

<sup>1326</sup> Stamer, “Concentrations of tramadol”, fn. 1323, above, at p. 45.

- iii. Tramadol carries the additional risk of seizures<sup>1327</sup> and life-threatening hypoglycemia.<sup>1328</sup> These are not risks typically seen with other analgesics, opioids and non-opioids alike.
- iv. Zeng *et al.* found: “Among patients aged 50 years and older with osteoarthritis, initial prescription of tramadol was associated with a significantly higher rate of mortality over 1 year of follow-up compared with commonly prescribed nonsteroidal anti-inflammatory drugs, but not compared with codeine.”<sup>1329</sup>
- k. The Pharmaceutical Opioid Industry has relied on flawed and industry-influenced studies regarding the risk of addiction from prescription opioids. The studies relied on by Defendants to estimate the risk of addiction from prescription opioids provide a significant underestimation of the true risk of misuse, dependence, and addiction for several reasons:
  - i. Many studies, particularly trials conducted by opioid manufacturers, screen out patients at higher risk of addiction, who are not commonly screened from real world clinical exposure.
  - ii. Many studies are not designed *a priori* to identify addiction outcomes, which means that they lack methodology to diagnose or otherwise accurately account for the cases.
  - iii. Many studies are sponsored and/or written by industry authors, raising conflict of interest and bias issues.
  - iv. Many studies are too short to assess addiction risk (as discussed previously).
  - v. Many studies do not use rigorous detection methods.
    - A. Most studies rely solely on patient questionnaire responses to identify problematic behavior, despite generally accepted knowledge that a significant subset of respondents will not disclose behaviors of interest that could subject them to stigma, sanction, or both, as exemplified by the Fleming study (discussed above, and below).
    - B. A retrospective study of urine toxicology information for 122 patients maintained on chronic opioid therapy, found that 43% of patients had a “problem” with opioids: positive urine

<sup>1327</sup> Ryan NE, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clinical Toxicology* 2015;53:545-550, at p. 545.

<sup>1328</sup> Fournier J-P, *et al.* Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain. *JAMA Intern Med.* 2015;175(2):186-193, at p. 186.

<sup>1329</sup> Zeng C, *et al.* Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA* 2019;321(10):969-982, at p. 969.

toxicology or one or more aberrant drug taking behaviors. The authors concluded “Monitoring both urine toxicology and behavioral issues captured more patients with inappropriate drug-taking behavior than either alone. Requiring a report of behavioral issues and urine toxicology screens for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone.”<sup>1330</sup>

C. Urine drug tests provide more reliable evidence of drug misuse and addiction than patient report. Fleming found a 24% rate of positive toxicology tests for illicit drugs. “Eighty-four of 185 (46%) patients with positive toxicology testing denied illicit drug use during the research interview, even when they were guaranteed anonymity. This finding confirms clinical observations that patients with chronic pain often mislead their physicians about illicit drug use . . . . Minimization of drug use and drug problems by patients is a major concern in all studies that try to estimate rates of addiction, especially for illegal drugs.”<sup>1331</sup> In other words, rates of opioid use disorder were potentially 8 times higher in the same population when objective measures of urine drug screens were used.

D. Databases with information on prescribing of controlled substances provide more reliable evidence of drug misuse and addiction than patient report. Checking a database with access to this information gives more reliable evidence on duplicate prescriptions, early refills, “doctor shopping,” and other indicators of misuse and addiction.<sup>1332</sup>

1. A particularly flawed article is the 2008 review by Fishbain, which claimed that the risk of addiction from chronic use of prescription opioids is 3.27% overall; 0.19% if considering de novo opioid users only.<sup>1333</sup> Overall, Fishbain included 67 studies in his review and analysis of various measures of addiction or abuse. With respect to the 3.27% / 0.19% addiction rates, Fishbain stated that he relied on a subset of 24 studies with a total of 82 addiction cases among 2,507 patients, identified in Appendix 1 to the article, accessed at the journal website. However, review of the Appendix 1 table shows only 23 studies with 81 addiction cases among 2173 patients, resulting in a prevalence of 3.73%,

<sup>1330</sup> Katz NP, Sherburne S, Beach M, *et al.* Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth. Analg.* 2003. doi:10.1213/01.ANE.0000080159.83342.B5, at p. 1097.

<sup>1331</sup> Fleming, *et al.* “Substance Use Disorders,” fn. 1242, above, at pp. 580-581.

<sup>1332</sup> Centers for Disease Control and Prevention, What States Need to Know about PDMPs. <https://www.cdc.gov/drugoverdose/pdmp/states.html>.

<sup>1333</sup> Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? a structured evidence-based review. *Pain Med.* 2008; 9(4):444-459. doi:10.1111/j.1526-4637.2007.00370.x, at p. 444.

rather than 3.27%. These figures are not reliable indicators of true prevalence of OUD, for the reasons explained below.

- i. The Fishbain analysis included studies that (a) were too short to accurately assess addiction risk; (b) administered low doses; (c) screened out patients at higher risk of addiction; (d) were not designed to identify addiction; (e) did not apply rigorous detection methods; and (f) were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
- ii. Fishbain's pooled analysis found substantially higher evidence of drug misuse/addiction (14.5%) when findings were based on the more objective measure of aberrant urine toxicology screens.<sup>1334</sup>
- iii. Fishbain's 2008 review omitted two studies from his 1992 review that had reported substantially higher prevalence than the pooled figure of 3.27% stated in the 2008 article. Studies by Evans, *Anesthesia* 1981; 36:597-602,<sup>1335</sup> (reported 16% addiction in Fishbain's 1992 article<sup>1336</sup>), and Katon, *Am J Psychiatry* 1985; 142:1156-60, (reporting 18.9% addiction),<sup>1337</sup> both appeared in Fishbain 1992 but were omitted from Fishbain 2008. Further, the Evans study, in turn, cited to an article by Maruta, *Mayo Clinic Proceedings* 1976; 54:241-4,<sup>1338</sup> which reported an incidence of 24% addiction among a chronic pain population.<sup>1339</sup> Fishbain 2008 stated that his search for relevant articles went back to 1966, so these three references would have been within the time period he searched. Fishbain was a litigation consultant for Defendant Purdue between at least 2005-2008, a relationship that was not disclosed in the 2008 article, and which casts the exclusion of the higher prevalence studies in a disturbing light.<sup>1340</sup> Equally troubling, Fishbain served as a

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<sup>1334</sup> *Id.* at p. 450.

<sup>1335</sup> Evans PJD. Narcotic addiction in patients with chronic pain. *Anaesthesia*. 1981;36(6):597-602. doi:10.1111/j.1365-2044.1981.tb10323.x.

<sup>1336</sup> The Evans article states that the addiction rate was 7%, which appears to be based on 9 cases among the full study population of 130 subjects. (Evans at p. 600) Fishbain's 1992 article states, "Of 56 chronic *benign* patients, 9 or 16% exhibited features of addiction." (Fishbain 1992, Table 4, at p. 83; emphasis added). Thus, comparing the two articles, it appears that Evans included the 74 cancer patients, who had no reported cases of addictive behavior, in the total of 130 subjects. Conversely, Fishbain 1992 limited his study to "Drug Abuse, Dependence, and Addiction in *Chronic Pain Patients*," (emphasis added); thus the figure of 16% (9/56) appears accurate.

<sup>1337</sup> Egan K, Katon W. Chronic Pain: Lifetime Psychiatric Diagnoses and Family History. *Am J Psychiatry*. 1985;(October):1156-1160, at p. 1157.

<sup>1338</sup> Note that the Maruta article was actually published in 1979, and the cite in the Evans article lists the incorrect year of publication.

<sup>1339</sup> Maruta T., Swanson D., Finlayson, R. Drug Abuse and Dependence in Patients with Chronic Pain. *Mayo Clin. Proc.* 1979 (April):241-244, at p. 242.

<sup>1340</sup> *Graves v. Purdue Pharma Ltd., et al.* Rule 26(a)(2) Disclosure of David A. Fishbain, MD, Civil Action 2:07cv107-MPM-SAA (USDC NMS), see p. 8 listing two additional Purdue cases where Fishbain was deposed as an expert witness.

presenter at Continuing Medical Education “opioid dinner dialogues” and audioconferences sponsored by defendant opioid manufacturer Endo in 2008, another undisclosed conflict of interest.<sup>1341</sup>

- iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, “According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, *i.e.*, addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients.”<sup>1342</sup> The same article also stated, “It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other ‘addiction’ studies described earlier, as they are both within the prevalence percentages derived from these studies.”<sup>1343</sup> However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain’s 2008 analysis.
- v. Also, Fishbain’s 2008 review<sup>1344</sup> included data from a 1992 study by Bouckoms, *et al.*, which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for “narcotics addiction.”<sup>1345</sup> Bouckoms also stated: “The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively.”<sup>1346</sup> Notably, the 0.03% figure in Bouckoms’ text is based on the Porter and Jick 1980 Letter<sup>1347</sup> – the only one of the 5 references that was *not* based on a population of patients treated with opioids for chronic pain.
- vi. All of the sources cited by Bouckoms were available to Defendants from 1992 on. Yet their promotional statements beginning in the 1990s cited the inapt Porter and Jick study<sup>1348</sup> of hospitalized patients with any exposure to opioids, regardless of duration, as the source for the

<sup>1341</sup> ENDO-FLAG-00421543; ENDO-FLAG-00421545; ENDO-FLAG-00306923

<sup>1342</sup> Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain*. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.

<sup>1343</sup> *Id.* at p. 81.

<sup>1344</sup> Fishbain, *et al.*, “What Percentage,” fn. 1333, above.

<sup>1345</sup> Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Ann Clin Psychiatry*. 1992. doi:10.3109/10401239209149570, at p. 185.

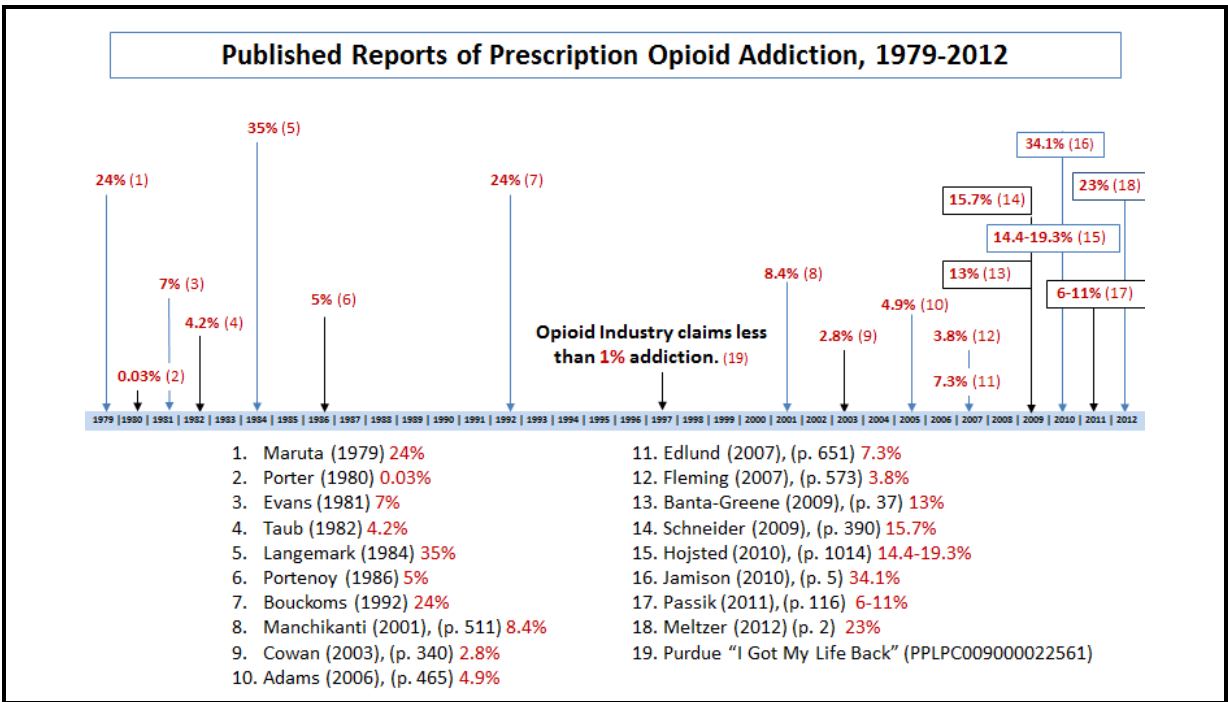
<sup>1346</sup> *Id.* at p. 188.

<sup>1347</sup> Porter and Jick, “Addiction Rare,” fn. 241, above, at p. 123.

<sup>1348</sup> *Id.*

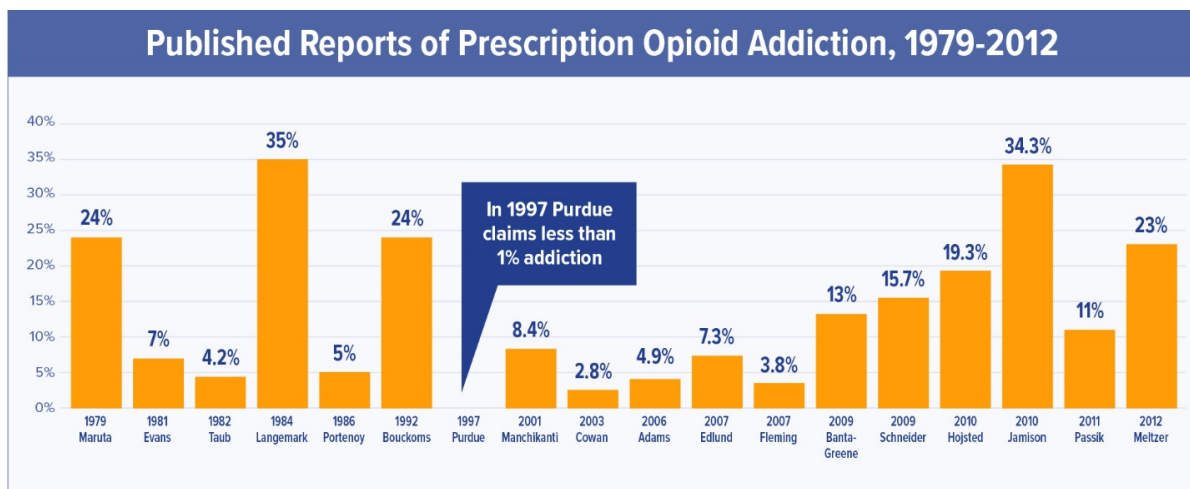
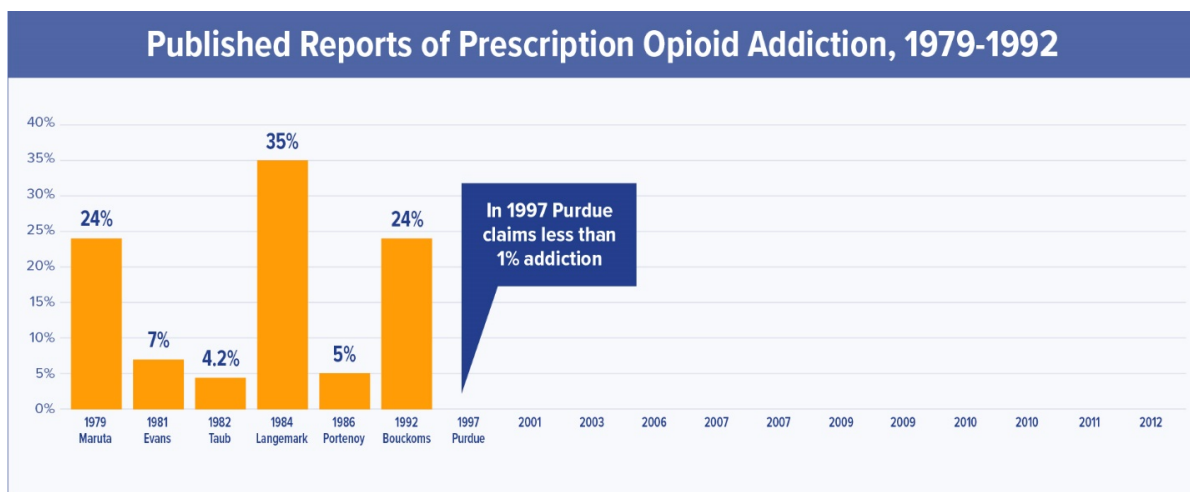
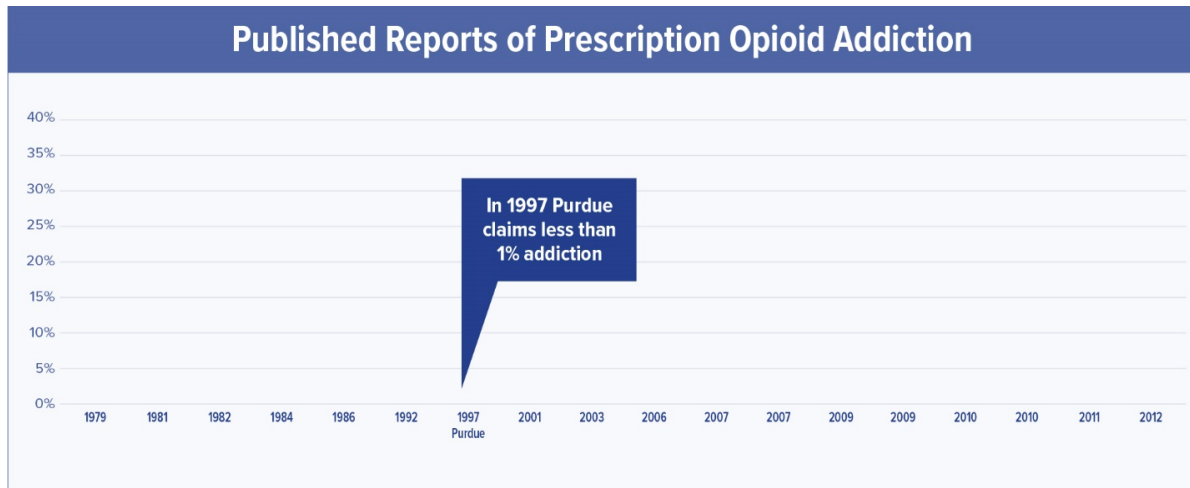


claim of “less than one percent” prevalence of addiction. I am not aware of any Defendants having issued a promotional statement citing the results of 24%, 4.2%, 7%, 35% or 5%, referenced by Bouckoms in 1992.<sup>1349</sup> Nor am I aware of any such statements by Defendants that cited the range of “prevalence from 3.2% to a high of 16% for the possibility of addiction” reported by Fishbain in 1992.<sup>1350</sup> The timeline below shows the dates of publications demonstrating far greater risks of addiction to prescription opioids than those misrepresented by Defendants. Further, the timeline below, and the summary demonstratives that follow, illustrate that risks were known and published in the peer-reviewed literature well before the 1990s, when the Pharmaceutical Opioid Industry began their misleading marketing of addiction rates that were “less than 1%,” “rare,” “nonexistent,” or “negligible” (see references at §8, below):



<sup>1349</sup> Bouckoms, *et al.*, “Chronic Nonmalignant,” fn. 1345, above, at p. 188.

<sup>1350</sup> Fishbain, *et al.*, “Drug Abuse,” fn. 1342, above, at p. 80.

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- vii. Fishbain made an admittedly “arbitrary” decision to apply a 65% “quality score” requirement, despite his own reference to a source

stating that studies with scores below 50% are generally not used.<sup>1351</sup> The Tables in the Appendix to the Fishbain 2008 article provide the quality scores only for the studies that were included, but not for those that were excluded, so it cannot be determined whether the three higher prevalence studies were excluded for failure to meet the arbitrary quality score threshold, or for other reasons. Their absence from the 2008 review casts further doubt on its reliability.

- m. Another flawed and biased study that was reviewed by Fishbain was co-authored by Portenoy.<sup>1352</sup> In this study, 27 physicians who attended training sessions to serve on “a pain-oriented speakers’ bureau” applied a “Pain Assessment and Documentation Tool” (PADT) to 388 of their patients, with diverse pain syndromes, who had been on various regimens of chronic opioid therapy for at least 3 months.<sup>1353</sup> The physicians reported their assessment that 5.93% (23/388) of their patients were addicted.<sup>1354</sup> However, the doctors also reported that 19.3 % (75/388) engaged in 3 or more “aberrant drug-taking behaviors,” such as requests for early renewals, increasing doses without authorization, reporting lost or stolen prescriptions, obtaining medications from other doctors, declining physical/social/psychological function, over-sedation, etc.; and that 10.8% (41/388) engaged in 5 or more such behaviors.<sup>1355</sup> Their conclusion of 5.93% addicted lacks validity for several reasons.
  - i. Appendix 1 states: “Of the total sample 5.93% were thought to demonstrate opioid prescription abuse/addition [sic].”<sup>1356</sup> This is not correct, since the 5.93% applies solely to addiction, whereas the abuse rates were much higher, as described above.
  - ii. Other studies on Fishbain’s reference lists would count such behaviors as evidence of addiction, such that the addiction rate in the Passik study would be about 2 to 4 times greater than the 5.93% rate based on the doctors’ reports. Including the full range of opioid use disorder (mild, moderate, severe) based on DSM-5 criteria, this study’s summative results (5.93% + 19.3% +10.8%) demonstrate that 36.06% of patients met DSM-5 criteria for opioid use disorder, approximating the 40% rate of opioid use disorder consistent with the Boscarino, *et al.* study<sup>1357</sup> described above.

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<sup>1351</sup> Fishbain, *et al.*, “What Percentage,” fn.1333, above, at p. 448.

<sup>1352</sup> Passik SD, Kirsh KL, Whitcomb L, *et al.* Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool. *J Opioid Manag.* 2005.

<sup>1353</sup> *Id.* at p. 258.

<sup>1354</sup> *Id.* at p. 263.

<sup>1355</sup> *Id.* at pp. 260-261.

<sup>1356</sup> *Id.* at Appendix I, p. 47.

<sup>1357</sup> Boscarino, *et al.*, “Opioid-use disorder,” fn. 1248, above, at p. 83.

- iii. The possibility of underestimating the addiction rate is of particular concern in light of the participating physicians' roles as Speakers' Bureau trainees.
- n. In yet another flawed study reviewed by Fishbain *et al.*, 10 patients, who had been treated for chronic noncancer pain (CNCP) with morphine for an average of 2 years, participated in a study alternating between one 60 hour period of morphine and one 60 hour period of placebo (two and a half days each).<sup>1358</sup> "When asked 'Do you have any drug craving?' (graded as mild, moderate or severe), no patients reported craving for morphine or a compulsion to take any," during the period of cessation of opioids.<sup>1359</sup> The authors concluded from these data "that there exists a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use."<sup>1360</sup> Appendix 1 states: "0% demonstrated psychological dependence."<sup>1361</sup> This conclusion lacks validity for several reasons.
  - i. The short duration without opioids is insufficient to assess "problematic opioid drug use." This methodology might detect physical dependence and withdrawal, but not addiction. Addiction is a chronic relapsing and remitting illness evidenced by a pattern of behavior over weeks to months, not hours to days.
  - ii. Craving and withdrawal are very subjective and not diagnostic of addiction. Further, asking study subjects about "craving" is likely to bias their response: "craving" is a loaded term associated with addiction. Patients would be savvy enough to want to avoid this pejorative label.
  - iii. This British study was funded by Janssen-Cilag, introducing inherent bias.<sup>1362</sup>
  - iv. Although this is a small study that would have little overall impact on the pooled analysis, it is worth attention if only to demonstrate the contradiction between Fishbain's inclusion of an almost absurdly brief study of 60 hours of exposure, while omitting relevant studies with higher prevalence that he personally cited in his earlier review article.

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<sup>1358</sup> Cowan DT, Wilson-Barnett DJ, Griffiths P, Vaughan DJA, Gondhia A, Allan LG. A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med.* 2005. doi:10.1111/j.1526-4637.2005.05020.x, at p. 113.

<sup>1359</sup> *Id.* at p. 116.

<sup>1360</sup> *Id.* at p. 119.

<sup>1361</sup> *Id.* at Appendix 1.

<sup>1362</sup> *Id.* at p. 113.

- o. Higgins, *et al.*, performed a meta-analysis of incidence of addiction studies, that is, addiction diagnosed in a pre-specified period of time following the initial exposure to a prescription opioid. The authors argued for a 4.7% overall incidence of iatrogenic addiction to prescription opioids,<sup>1363</sup> but their findings need to be considered in light of a number of limitations.
  - i. Higgins did not account for the role of dose and duration as the main cause of opioid use disorder. In particular, Higgins claimed to rely on the Edlund (2014) study for an incidence rate of 0.2%, while omitting Edlund's finding that the rate in his healthcare database study was 50 times higher for those who were exposed to chronic (>90 days) high dose (>120 MME), compared to patients with only acute exposures (over 6% for the former, compared to 0.12% for the latter). Edlund noted that it was "almost meaningless to talk of a single 'rate'"<sup>1364</sup> under these circumstances, yet that is precisely what Higgins did. Similarly, Higgins cited the Cepeda (2013) study for an overall rate of 0.5%, ignoring that this healthcare database study included all patients who "initiated" opioid therapy, without analysis of variations in rates between patients with different doses and durations of exposure.
  - ii. Incidence will inevitably under-report the number of cases in a population, because it will only examine data for a fixed beginning and endpoint; whereas prevalence is the more accurate marker of the number of cases existing in a population at a given point in time, including all cases of addiction among the population taking prescription opioids. This is an important point, since a majority of OUD-diagnosed patients have recent medical prescriptions for opioids,<sup>1365</sup> such that their prescriptions are maintaining or contributing to their disorders, regardless of when onset of OUD occurred.<sup>1366</sup>
  - iii. New onset opioid use disorder (incidence) does not take into account the harm done to patients who maintain or relapse to opioid addiction as a result of medical exposure to opioids. That is, continued exposure imposes continued risk of misuse, dependence, overdose, and the panoply of ill effects of chronic opioid therapy described herein.
  - iv. The authors speculate that the pooled rate was higher for the studies of "weak" opioids than for "strong" opioids because the subjects might

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<sup>1363</sup> Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth.* 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009, p. 1339.

<sup>1364</sup> Edlund, "Role of Opioid Prescription", fn. 75, above, at p. 562.

<sup>1365</sup> Ali, "Opioid Use Disorder", fn 83, above, at p. 156.

<sup>1366</sup> *Id.* at p. 164.

have displayed “pseudoaddiction,”<sup>1367</sup> *i.e.*, because the opioids were weak, they displayed drug-seeking behaviors to alleviate their pain that were misconstrued by the physicians, rather than because of a use disorder. The report of a higher rate with lower doses is an unreliable, outlier finding that contradicts numerous large, well-done studies demonstrating the dose-response relationship between higher opioid dose and greater addiction and mortality. Also, Higgins’ comparison of “weak” versus “strong” opioids failed to meet standard methods of comparing the dose of prescription opioids according to their milligrams morphine equivalent, or MME.

- v. The authors’ restrictive criteria resulted in only 12 studies having been included<sup>1368</sup> compared to others (*e.g.*, Vowles), who included 38 studies.
- vi. The authors erroneously stated that Vowles reached a similar conclusion as to the rates of addiction (4.3 v. 4.7%),<sup>1369</sup> when in fact Vowles reported rates of addiction as 8-12%,<sup>1370</sup> or approximately 21-29% when the spectrum of mild through severe OUD is included.
- vii. Two of three authors report pharma consulting, including Pfizer.<sup>1371</sup>
- p. The 2010 Cochrane Review by Noble *et al.* (2010), stated that opioid addiction occurred in “0.27% of participants in the studies that reported that outcome,”<sup>1372</sup> and “... serious adverse events, including iatrogenic opioid addiction, were rare.”<sup>1373</sup> However, the underlying studies in the Cochrane Review that were selected for analysis were predominantly funded by the manufacturers and were neither intended nor designed to detect addiction risks. As detailed below, estimates based on those studies are unreliable and unrealistically low.
- i. The Cochrane 2010 review analyzed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty five of the studies were case series or uncontrolled long-term trial continuations. The other was an RCT comparing two opioids.<sup>1374</sup> Only 8 of the 26

<sup>1367</sup> Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth.* 2018;120(6):1335-1344. doi:10.1016/j.bja.2018.03.009. at p. 1343.

<sup>1368</sup> *Id.* at p. 1335.

<sup>1369</sup> *Id.* at p. 1342.

<sup>1370</sup> Vowles, *et al.*, “Rates of Opioid Misuse,” fn. 1224, above, at p. 569; McNicol, *et al.*, Cochrane Review 2013, fn. 1135, above, at p. 28.

<sup>1371</sup> Higgins, *et al.*, “Incidence of Iatrogenic,” fn. 1363, above, at p. 1343.

<sup>1372</sup> Noble, *et al.*, “Long Term Opioid Management,” fn. 1120, above, at p. 9.

<sup>1373</sup> *Id.* at p. 2.

<sup>1374</sup> *Id.* at p. 1.



included studies provided data on addiction: Allan; Anderson; Hassenbusch; McIlwain; Milligan; Mystakidou; Portenoy; and Zenz.

- ii. Only one of these studies (Portenoy, 2007)<sup>1375</sup> was *a priori* designed to assess risk of opioid use disorder/addiction. The rest were designed to assess pain efficacy, and addiction risk was an afterthought. Further, none applied rigorous detection methods, or in most cases any detection methods at all to assess opioid misuse or addiction. All of the studies excluded patients with a history of alcohol or substance use disorders. Seven of the eight studies were sponsored and/or written by industry authors, raising conflict of interest and bias issues.
- iii. Below, I address in detail each of the eight studies providing data on addiction that were included in the 2010 Cochrane Review.
  - A. Allan *et al.* compared efficacy and safety of transdermal fentanyl and sustained release morphine in opioid naïve patients with chronic low back pain over 13 months.<sup>1376</sup> Classification as “opioid naïve” was based on the patient receiving limited opioids in the 4 weeks prior to the study, with no screening for opioid use prior to 4 weeks.<sup>1377</sup> Opioid misuse and addiction did not warrant listing in the Adverse Event “Table 8.”<sup>1378</sup> In other words, it was not a variable the authors were measuring, as corroborated by the absence of any instrument to assess addiction, despite the use of other survey questionnaires used to track other adverse events.
    - I. Yet the authors claimed “Addiction was not reported as an adverse event for any participant.”<sup>1379</sup> The authors further stated “No cases of addiction were reported as an adverse event; this is in line with other studies, which have shown that opioids can be used in chronic noncancer pain without significant risk of abuse. [citing Jamison *et al.*, *Spine* 1998].”<sup>1380</sup>
    - II. The authors’ conclusions are not reliable based on methodologic inadequacies to assess for addiction risk. Even when investigators are attempting to detect addiction and abuse, as in the studies described above,

<sup>1375</sup> Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007; 23: 287-299, DOI: 10.1097/01.brs.0000186860.23078.a8.

<sup>1376</sup> Allan L, Richarz U, Simpson K, Slappendel R. Transdermal Fentanyl Versus Sustained Release Oral Morphine in Strong-Opioid Naïve Patients With Chronic Low Back Pain. *Spine* 2005; 30(22):2484-2490, at p. 2484.

<sup>1377</sup> *Id.* at p. 2485.

<sup>1378</sup> *Id.* at p. 2488.

<sup>1379</sup> *Id.*

<sup>1380</sup> *Id.* at p. 2489.

the difficulties are daunting, as indicated by reports of patient concealment of problem behaviors and substantial disparities between questionnaire responses and urine drug screening; when researchers do not look for addiction and abuse, they are quite unlikely to find such evidence. Further, the study was underwritten by Janssen pharmaceuticals, the makers of Duragesic, transdermal fentanyl, suggesting bias conferred by industry sponsorship.<sup>1381</sup>

- B. Anderson *et al.* followed 30 patients prospectively for 24 months to assess the long-term safety and efficacy of chronic intrathecal morphine (injected into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid) in the treatment of chronic pain.<sup>1382</sup> Patients with “psychopathological or substance abuse problems” were screened out and deemed ineligible. Questionnaires were used to track many different variables, but none asked about signs and symptoms of opioid use disorder.
  - I. The authors report that one patient (1/30, 3%) “was withdrawn from therapy because of drug-seeking behavior . . . .”<sup>1383</sup> This patient “complained of continually escalating pain after infusion system implant, despite successful pain relief during trial at an epidural dose of less than 10mg per day . . . and sought to obtain oral narcotics from other health care providers,” although the authors do not disclose how they obtained this information. When further requests for dose increases were denied, the patient dropped out of the study.<sup>1384</sup>
  - II. The authors conclude “In general, the incidence of addiction among patients with nonmalignant pain receiving chronic opioid is low,” but their findings are unreliable given methodological failures to assess addiction risk. The study was sponsored by Medtronic, Inc., the makers of the intrathecal pump.<sup>1385</sup>

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<sup>1381</sup> *Id.* at p. 2484.

<sup>1382</sup> Anderson VC, Ph D, Burchiel KJ. Prospective Study of Long-term Intrathecal Morphine in the Management of Chronic Nonmalignant Pain. *Neurosurgery* 1999;44(2), at p. 289.

<sup>1383</sup> *Id.* at p. 292.

<sup>1384</sup> *Id.* at pp. 295-296.

<sup>1385</sup> *Id.* at p. 299.

- C. Hassenbusch, like Anderson, examined a case series of patients (22) with intrathecal opioid infusion pumps. In this case, they followed patients for 5 years.<sup>1386</sup> The same limitations described in the Anderson study apply here: patients with history of mental illness or addiction were excluded,<sup>1387</sup> and there were no screening instruments or any other detection method to assess for opioid misuse or addiction. Yet the authors conclude “There was no occurrence of opioid dependence, either physical or psychological . . . .”<sup>1388</sup>
- D. McIlwain *et al.* did a 52-week open label extension study of oxymorphone extended release (ER) in patients with moderate to severe chronic osteoarthritis related pain.<sup>1389</sup> The study was sponsored by Endo Pharmaceuticals, the makers of the study drug.<sup>1390</sup> The study did not use screening instruments or other detection methods for opioid misuse or addiction. Their Table 2 of adverse events did not include opioid misuse/addiction, despite including 11 other opioid-related adverse events.<sup>1391</sup> Despite the absence of any method for detecting or measuring addiction risk, the authors concluded, “No instances of drug addiction or abuse were recorded.”<sup>1392</sup>
- E. Milligan *et al.* studied 532 chronic noncancer pain patients (only 301 completed the trial) being treated with transdermal fentanyl for up to 12 months. They report “drug abuse/dependence” in less than 1% of their sample, but qualify this by saying, “none was considered definitely related to the treatment.”<sup>1393</sup> Like the other studies included in the addiction risk assessment of the 2010 Cochrane review, this study was not designed to reliably assess addiction risk: patients with a history of substance abuse or psychiatric

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<sup>1386</sup> Hassenbusch S, Stanton-Hicks M, *et al.* Long Term Intraspinal Infusions Of Opioids in the Treatment of Neuropathic Pain. *Journal of Pain and Symptom Management*. 1995;10:527-543, at p. 529.

<sup>1387</sup> *Id.* at p. 528.

<sup>1388</sup> *Id.* at p. 536.

<sup>1389</sup> McIlwain H, Ahdieh H. Safety, Tolerability, and Effectiveness of Oxymorphone Extended Release for Moderate to Severe Osteoarthritis Pain A One-Year Study. *Am J Ther*. 2005;112:106-112, p. 106.

<sup>1390</sup> *Id.* at p. 111.

<sup>1391</sup> *Id.* at p. 108.

<sup>1392</sup> *Id.* at p 109.

<sup>1393</sup> Milligan K, Lanteri-minet M, Borchert K, *et al.* Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain. *J Pain*. 2001;2(4):197-204 at p. 197, doi:10.1054/jpai.2001.25352.

disorders were excluded, no screening or detection instruments for opioid misuse or addiction were described.<sup>1394</sup>

- I. The authors report three cases of “drug abuse (2 moderate and 1 severe)”; two cases of “moderate physical drug dependence (as opposed to abuse)”; and “no reports of addiction.”<sup>1395</sup> Yet how these concepts were defined and the cases detected are not clarified.
  - II. The study was supported by a grant from Janssen.<sup>1396</sup> Despite these serious flaws, the authors concluded, “There were no reports of addictive behavior in any of the patients during this long-term study. Because the fear of addiction is one of the reasons for the underuse of opioids in chronic noncancer pain, this study provides further evidence that these fears are unfounded.”<sup>1397</sup> This conclusion does not follow from the evidence.
- F. The study by Mystakidou recruited 529 patients into an open-label study of transdermal therapeutic system-fentanyl (TTS-F) for 28 days, followed by an open-label follow-up for a median of 10 months between 1996-2002.<sup>1398</sup> The first page of the article includes the copyright symbol for the American Pain Society, which had been funded substantially by opioid manufacturers; the authors do not disclose a corporate sponsor, but they cite to prior studies of Dellemijn and Allan that acknowledged participation by Janssen-Cilag, the manufacturer of Duragesic TTS-F, and the Janssen Research Foundation.<sup>1399</sup>
- I. A complete description of exclusion criteria was not provided; the authors stated only, “Exclusion criteria included a history of opioid abuse, surgery in the preceding 7 days or scheduled surgery, contraindications to opioids, and opioids use outside of the designated treatment regimen.”<sup>1400</sup> No information is provided as to what constituted “contraindications to opioids;” and

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<sup>1394</sup> *Id.* at p. 198.

<sup>1395</sup> *Id.* at pp. 201-202.

<sup>1396</sup> *Id.* at p. 197.

<sup>1397</sup> *Id.* at p. 203.

<sup>1398</sup> Mystakidou K, *et al.* Long-Term Management of Noncancer Pain With Transdermal Therapeutic System-Fentanyl. *J Pain.* 2003;4(6):298-306. doi:10.1016/S1526-5900(03)00632-1, at pp. 298-299.

<sup>1399</sup> *Id.* at p. 305.

<sup>1400</sup> *Id.* at p. 299.

the exclusion for “opioids use outside the designated treatment regimen” inherently eliminates the population with the most obvious defining characteristic of addiction.

- II. The authors state, “Following discontinuation from the study, no patient complained of withdrawal symptoms or was found to display dependency”<sup>1401</sup>; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.
- G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (OxyContin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain.
- I. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy.
  - II. The authors reported “6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse.”<sup>1402</sup> This appears to be the basis for the “3%” figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, “Patients with self-reported past or present substance or alcohol abuse” were excluded, as were patients with a

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<sup>1401</sup> *Id.* at pp. 300-301.

<sup>1402</sup> Portenoy, *et al.*, “Long Term Use,” fn. 1375, above, at p. 296.

“documented allergy to oxycodone or other opioids.”<sup>1403</sup>  
 Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.<sup>1404</sup>

- H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.<sup>1405</sup> Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were discontinued for “lack of compliance;” and 8 died during the study period).<sup>1406</sup>
- I. Zenz reported, “There were no cases of respiratory distress or addiction to opioids.”<sup>1407</sup> As in the studies described above, Zenz had no protocol to look for or record addiction or abuse.
- II. No details were provided as to the type of “noncompliance” that caused 10 patients to be discontinued, but “noncompliance” in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.
- iv. In summary, the studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy, lack of any method to detect addiction or misuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.
- v. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled “Addiction Rare in Patients Treated with Narcotics,” reported only four cases of addiction among 11,882 patients treated with opioids.<sup>1408</sup> This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent. Nonetheless, it influenced prescribers and was frequently

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<sup>1403</sup> *Id.* at p. 288.

<sup>1404</sup> *Id.* at p. 287.

<sup>1405</sup> Zenz M, *et al.* Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. *J Pain Symptom Manage.* 1992;7(2):69-77, at p. 70.

<sup>1406</sup> *Id.* at p. 73.

<sup>1407</sup> *Id.* at p. 69.

<sup>1408</sup> Porter and Jick, “Addiction Rare,” fn. 241, above, at p. 123.



quoted by the Pharmaceutical Opioid Industry in its advertisements for opioids in the treatment of chronic pain, as proving that “less-than-1%” of patients receiving opioids for pain becomes addicted. Defendants’ promotional messages continued to cite their “less-than-1%” claim, or that addiction with chronic opioid therapy was “rare,” despite numerous peer-reviewed studies to the contrary over a period of decades. (*See* Appendix I.)

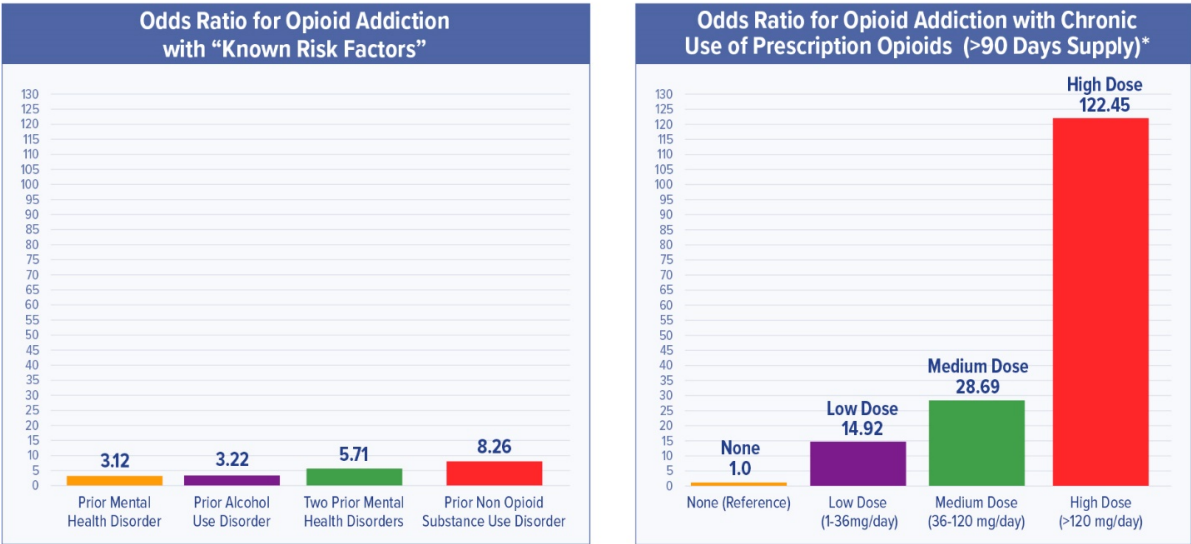
- q. In summary, there is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, “rare,” or “less than 1%.” In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 30%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction.
- r. The Pharmaceutical Opioid Industry also made inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.
- i. Over the years of increased use of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop “screening” instruments that might identify patients at high risk of addiction, who could then be screened out of opioid therapy, or closely monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odds ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odds ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).<sup>1409</sup> For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs

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<sup>1409</sup> Edlund, *et al.*, “Role of Opioid Prescription,” fn.75, above, at p. 563.

than the existence of identifiable risk factors for OUDs. These data are shown in the graphs below:

**DOSE AND DURATION OF PRESCRIPTION OPIOIDS ARE THE STRONGEST RISK FACTORS FOR OPIOID ADDICTION**



SOURCE: Edlund 2014

\*All doses calculated as Morphine Milligrams Equivalent, or "MME"

- ii. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is prescribing.<sup>1410</sup> These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then there will never be a failsafe method.
- iii. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the

<sup>1410</sup> Weisner CM, Campbell CI, Ray GT, *et al.* Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293, p. 292.

progress in a narrative review as follows: “Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy.”<sup>1411</sup>

- iv. Chou *et al.*, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported “inconsistent results” for the 10-item Opioid Risk Tool and that “No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.”<sup>1412</sup>
- v. Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could “safely” be prescribed opioids, has recently been invalidated. “In this population, we were not able to replicate the findings of the initial ORT study. Self-report was *no better than chance* in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT).”<sup>1413</sup>
- vi. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent risk associated with opioids themselves, has been prevalent among prescribers in the 1980s, 1990s, and 2000s who were encouraged by the Defendants to rely on such tools, and it is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction. For example, Janssen also promoted the concept that “the potential for addiction is in the patient, not the opioid” and defined high risk as “long-term exposure to opioids in addicts.”<sup>1414</sup> Both of these statements are false and misleading: opioids

<sup>1411</sup> Kaye A, Jones M, Kaye A, *et al.* Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Title. *Pain Physician J.* 2017, at p. 573. This conclusion was reaffirmed in a very recent review that concluded: “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, *demonstrated poor performance in helping to identify patients at high vs low risk.*” Klimas, *et al.*, Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. *JAMA Netw Open.* 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365.

<sup>1412</sup> Chou, *et al.*, “Effectiveness and Risks – Systemic,” fn. 1119, above, at p. 280.

<sup>1413</sup> Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.(emphasis added).

<sup>1414</sup> JAN-MS-00310473, produced in native at \*11-12.

are inherently addictive and long-term exposure is a significant risk factor even in patients without other risk factors for addiction. Also, as discussed in this Report, abundant scientific literature demonstrates that even short-term exposure will result in chronic use and its attendant problems of addiction and dependence in a significant subset of patients.

- vii. The impact of the dose-duration risks of prescribed opioids will be felt for years, as evidenced by a recent study of OUD among hospitalized chronic pain patients which found that “prevalence of OUD increased substantially from 2011 to 2015...increas[ing] from 109,222 in 2011 to 172,680 in 2015 ( $P < 0.001$ ).”<sup>1415</sup> As patients are exposed to opioids for longer durations, the risk for developing OUD rises.
- viii. Further, prescribers who relied on Pharmaceutical Opioid Industry statements regarding the great benefits and minimal risks of prescribing opioids for pain would also gain a false sense that there was little or no need for screening.
- ix. It is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (*See* discussion of Fleming study, above). As noted in a very recent *JAMA* review, “Despite their widespread use, most screening tools involving combinations of questions were based on low-quality studies or, when diagnostic performance was assessed among high-quality studies, demonstrated *poor performance in helping to identify patients at high vs low risk*.”<sup>1416</sup>
- x. Finally, Defendants were well aware that primary care physicians (PCPs), had neither the skills nor the resources to effectively monitor their patients for the development of opioid misuse and addiction, but nonetheless targeted these providers to promote sales.
  - A. At a 2001 Scientific Advisory Board meeting for Janssen Duragesic, it was evident that Janssen was targeting front line providers, i.e. PCPs to promote Duragesic.<sup>1417</sup>
  - B. At the same time and at the same meeting, Janssen and its advisors were well aware the PCPs were not adequately

<sup>1415</sup> Orhurhu V *et al.* Trends of opioid use disorder among hospitalized patients with chronic pain. *Pain Practice*. 2019;19(6): 656-663, at p. 656.

<sup>1416</sup> Klimas, “Strategies to Identify”, fn. 661, above, at p.1. (emphasis added).

<sup>1417</sup> JAN-MS-00481055

trained to track opioid misuse and addiction: “Physicians are writing more opioid prescriptions, but they do not know how to monitor patients.”<sup>1418</sup>

- C. Janssen’s own advisors conceded that even with training, it is extremely difficult to tell which patients will develop an opioid misuse problem: “Preliminary findings show that information or impressions gained in the doctor-patient relationship cannot predict which patients will have a positive urine toxicology screen. Even urine tox screens may not be reliable as they vary, and some have low sensitivities to oxycodone and fentanyl.”<sup>1419</sup>
- D. Yet despite these tangible and openly recognized limitations, Defendants launched an aggressive marketing campaign targeting prescribers, which misrepresented the facts on risk of addiction and validity of screening, and instead aggressively promoted uptitrating of their products.<sup>1420</sup>

**9. Increased supply of prescription opioids contributed substantially to more individuals becoming addicted to opioids and transitioning from prescription opioids to illicit sources of opioids such as heroin and fentanyl (The Gateway Effect).**

- a. There is a clear causal link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (“NMUPO”)<sup>1421</sup>, is defined as taking an opioid medication outside of a prescribed indication.<sup>1422</sup> With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer durations (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, addiction, and overdose death.<sup>1423</sup> These are the expected and natural consequences of exposing large populations to addictive and dangerous drugs, particularly where tolerance requires users to increase the dose to achieve the same effect, resulting in ever-greater risk of harm.
- b. Teens are especially vulnerable to the increased access to prescription drugs. Adolescence is a time when the rapidly growing brain is more plastic, and therefore more vulnerable on a neurological level, to potentially irreversible brain changes caused by chronic drug exposure. Teens are also more likely to

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<sup>1418</sup> *Id.* at 1062.

<sup>1419</sup> *Id.* at 1064.

<sup>1420</sup> See JAN-MS-00779345, FDA Warning Letter to Janssen, RE: NDA #19-813, September 2, 2004.

<sup>1421</sup> NMUPO is sometimes referenced as “NUPO”, nonmedical use of prescription opioids.

<sup>1422</sup> NASEM Report (2017), fn. 58, above, at p. 152.

<sup>1423</sup> *Id.* at p. 193

take risks, without appreciating the adverse consequences associated with those risks.<sup>1424</sup>

- c. In 2012, some 1.9 million individuals aged 12 or older misused a prescription drug for the first time within the past twelve months, an average of 1,350 initiatives per day. Prescription drugs now rank fourth among the most-misused substances in America, behind alcohol, tobacco, and cannabis. They rank second among teens. Of those who became addicted to any drug in the previous year, a quarter started out using a prescription medication: 17 percent began with opioid pain relievers, 5 percent with sedative-hypnotics, and 4 percent with stimulants.<sup>1425</sup>
- d. In 2017, McCabe *et al.* found, “Adolescents who reported both medical and nonmedical use of prescription opioids were more likely to indicate medical use of prescription opioids before initiating nonmedical use...” (“NUPO”)<sup>1426</sup> “The findings provide compelling evidence that medical use of prescription opioids and NUPO are highly correlated, especially among adolescents. . . . We found that the majority of NUPO involved a history of medical use, and this finding should provide some concern to health professionals who prescribe opioid medications to adolescents, given the serious health consequences associated with NUPO.”<sup>1427</sup> McCabe’s reference for this point included the Compton (2016) article (cited in §9.h., below), that described the trajectory from non-medical use to illicit opioids, thus emphasizing that McCabe is referring to the “Gateway Effect” transition, i.e., from initial medical use, to subsequent non-medical use, and ultimately to illicit opioids.
- e. In 2019, McCabe *et al.* found that almost one in every two high school seniors who reported the medical use of prescription opioids after initiating NMUPO had two or more substance use disorder (addiction) symptoms at age 35.<sup>1428</sup>
  - i. These data show that teens who are exposed to prescription opioids without a prescription will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life (above what their risk would have been with non-medical use alone). The cumulative effect of

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<sup>1424</sup> Lembke, Drug Dealer MD, fn. 3, above, at pp. 26 and 48.

<sup>1425</sup> *Id.* at pp. 25-26.

<sup>1426</sup> McCabe, Sean Esteban, *et al.* Trends in medical and nonmedical use of prescription opioids among US adolescents: 1976–2015. *Pediatrics* 139.4 (2017): e20162387, at p. 1.

<sup>1427</sup> *Id.* at p. 8.

<sup>1428</sup> McCabe SE, Veliz PT, Boyd CJ, Schepis TS, McCabe V V., Schulenberg JE. A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019. doi:10.1016/j.drugalcdep.2018.10.027, at p. 379.



prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction.<sup>1429</sup>

- ii. The authors write, “These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents.”<sup>1430</sup> While the authors suggest that screening can play a role in mitigating future opioid addiction, screening tools have been shown to have limited efficacy in identifying at risk patients.<sup>1431</sup> The more significant goal is to reduce access to prescription opioids, which increases risk by increasing exposure to both medical and subsequent non-medical use.
- f. In 2020, McCabe *et al.* reported upon the longitudinal relationship between U.S. teens’ prescription opioid use (medical and non-medical) and subsequent heroin use in adulthood.<sup>1432</sup> From more than 11,000 survey respondents, they found that adolescents who reported *either medical use or non-medical use* of prescription opioids were at greater risk of progressing to heroin use in adulthood than population controls.<sup>1433</sup>
- i. The McCabe 2020 study definitively supports the conclusion that medical users of prescription opioids transition to heroin use, regardless of intervening non-medical use. In more recent cohorts in the population sample in the McCabe 2020 study, 7% of teens who reported prescription opioid medical use only went on to use heroin in adulthood, for an adjusted odds ratio of 2.68 (95% CI 1.01, 7.17).<sup>1434</sup> This “compelling longitudinal data” showed that adolescents who reported medical use only of prescription opioids compared to adolescents who had never been exposed to prescription opioids “were nearly 3 times more likely to transition to heroin use in subsequent years.”<sup>1435</sup>

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<sup>1429</sup> *Id.* at p. 381.

<sup>1430</sup> *Id.* at p. 383.

<sup>1431</sup> Clark MR, Hurley RW, Adams MCB. Re-assessing the Validity of the Opioid Risk Tool in a Tertiary Academic Pain Management Center Population. *Pain Med.* 2018;19(7):1382-1395. <http://dx.doi.org/10.1093/pm/pnx332>, at p. 1382.

<sup>1432</sup> McCabe SE, Boyd CJ, Evans-Polce RJ, McCabe VV, Schulenberg JE, Veliz PT. From Pills to Powder: A 17-year transition from prescription opioids to heroin among US adolescents followed into adulthood. *J Addict Med.* 2021;15:241-244., at p. 241.

<sup>1433</sup> *Id.*

<sup>1434</sup> *Id.* at Table 2.

<sup>1435</sup> Compton WM, Lopez MF. Pathways to heroin use: Commentary on McCabe et al. *J Addict Med.* 2021;15(3):178-180, at pp. 178-179. Wilson Compton is the Deputy Director of the National Institute on Drug Abuse (NIDA), *see* <https://www.drugabuse.gov/about-nida/organization/offices/office-nida-director-od/biography-wilson-compton-md-mpe>

- ii. Further, McCabe *et al* report that among their sample population already using heroin by age 18 (n=179), 22% used heroin following non-medical use of prescription opioids, and 39% used heroin and prescription opioids non-medically within the same year and 13% misused prescription opioids after initiating with heroin.<sup>1436</sup> The increased access and supply of prescription opioids has increased the risk of teenagers and young adults being exposed to any opioid. Prescription opioid use and heroin use are inextricably intertwined.
- g. Writing in the journal *Pediatrics* (2018) Harbaugh *et al.* report that “The majority of US high school seniors with both medical use and nonmedical use of prescription opioids reported medical use before initiating nonmedical use of prescription opioids, suggesting a role of leftover prescriptions in the transition to a nonmedical use of prescription opioids. This may be due, in part, to the perception that prescription opioids are safe if they are prescribed by physicians despite the fact that the addiction potential is similar to heroin.”<sup>1437</sup>
- h. There is a clear causal link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids.
  - i. The natural history of the disease of addiction is that individuals with addiction require increasing amounts and/or more potent forms over time to overcome tolerance, to maintain physiologic homeostasis, and to avoid painful withdrawal.
  - ii. Scientific literature supports the conclusion that greater exposure to prescription opioids is associated with greater transition to heroin. An authoritative CDC study concluded, “Frequent nonmedical users - people reporting 100-365 days of PYNMU [Per Year Nonmedical Use] - had the highest rate of past year heroin use and were at increased risk for ever injecting heroin (aOR 4.3, 95% CI 2.5-7.3) and past year heroin abuse or dependence (aOR 7.8, 95% CI 4.7-12.8) compared to infrequent nonmedical users (1-29 days of PYNMU).”<sup>1438</sup> Note that this study relied on NSDUH data, which investigated only nonmedical users of prescription opioids; therefore the study does not mean that medical users are somehow immune to the risk of transition to heroin. To the contrary, as demonstrated by McCabe, subjects who had only reported medical use of prescription opioids experienced a statistically significant, 2.68-fold increased risk of transition to heroin use.<sup>1439</sup>

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<sup>1436</sup> McCabe, “From Pills to Powder”, fn. 1432, above, at p. 3.

<sup>1437</sup> Harbaugh CM, Lee JS, Hu HM, *et al.* Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics*. 2018;141(1):e20172439, at p. 5.

<sup>1438</sup> Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132(1-2):95-100, at p. 95.

<sup>1439</sup> McCabe, “From Pills to Powder”, fn. 1432, above, at Table 2.

- iii. The finding of greater transition to heroin with more prescription opioid use provides an example of a dose-response relationship between exposure to a risk factor and the occurrence of an adverse outcome, and such a dose-response relationship is a hallmark of cause and effect. Further, the adjusted Odds Ratio (aOR) of 4.3, as reported in the CDC study, above, falls within the range of “strong” associations, another indicator of cause and effect between exposure to prescription opioids and the outcome of heroin abuse. *See* Section §C.13 of this Report for a detailed discussion of the factors considered in determining whether an association is likely to be causal.
- iv. As increasing numbers of Americans became addicted to prescription opioids over the past two decades, they were forced to seek out cheaper and more potent opioids. The illicit drug market met that increased demand with cheap and available heroin and fentanyl. Fentanyl, which is 50-100 times more potent than heroin and comes in white powder form similar to heroin, made its way into the illicit market without users realizing what they were ingesting, resulting in a surge of fentanyl related overdose deaths.<sup>1440</sup>
- v. “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use<sup>1441</sup>...The interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”<sup>1442</sup>
- vi. In the 1960s, 80% of opioid users reported that their first exposure to opioids was in the form of heroin. By the 2000s, however, 75% of opioid users reported that their first exposure to opioids was in the form of prescription painkillers.<sup>1443</sup>
- vii. In a study based on NSDUH data from 2002-2011, the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.<sup>1444</sup>

<sup>1440</sup> “IMF [illicitly manufactured fentanyl] is most commonly mixed with or sold as white powder heroin.” Gladden RM, Martinez P, Seth P. Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid–Involved Overdose Deaths — 27 States, 2013–2014. *MMWR Morb Mortal Wkly Rep* 2016;65:837–843, at pp. 836, 840-841. DOI: [http://dx.doi.org/10.15585/mmwr.mm6533a2external icon](http://dx.doi.org/10.15585/mmwr.mm6533a2external%20icon).

<sup>1441</sup> NASEM Report (2017) at fn. 58, above at p. 215. *See also* discussion of Paulozzi (2006), *supra*, at §C.3.b.

<sup>1442</sup> *Id.* at p. 248.

<sup>1443</sup> Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014. doi:10.1001/jamapsychiatry.2014.366, at p. E-1.

<sup>1444</sup> Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Rev*. 2013;(August):1-16, at p. 1.

- viii. Prescription opioid use disorder/addiction is associated with a likelihood of heroin addiction that is 40 times as great as the likelihood with no prescription-opioid misuse or addiction, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.<sup>1445</sup>
- ix. Eighty-six percent of urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 had used prescription opioids nonmedically before using heroin.<sup>1446</sup> Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.<sup>1447</sup>
- x. Muhuri found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.<sup>1448</sup>
- xi. A study of heroin users in Wilmington, Delaware, found that “most reported that prescription opioids were indeed their gateway to heroin use.”<sup>1449</sup>
- xii. A 2014 research paper evaluating transitions from opioid pills to heroin injecting in Philadelphia and San Francisco, concluded that, “Unlike those substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”<sup>1450</sup>
- xiii. A recent article by Pielech, *et al.*, stated, “Emerging data indicate that any exposure to opioids as an adolescent (medical or non-medical) appears to present short and long term risks for initiating heroin and prescription opioid use.”<sup>1451</sup>

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<sup>1445</sup> Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med*. 2016. doi:10.1056/NEJMra1508490, at p. 157.

<sup>1446</sup> Lankenau SE, Teti M, Silva K, Bloom JJ, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy*. 2012;23(1):37-44, at p. 41.

<sup>1447</sup> Compton, *et al.*, “Relationship Between NPOU and Heroin Use,” fn. 1445, above, at p. 156.

<sup>1448</sup> Muhuri, *et al.*, “Associations of NMPRU and Heroin,” fn. 1444, above, at p. 1.

<sup>1449</sup> Inciardi JA, *et al.*, Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment. *Pain Medicine*. 2009;10:537-548, at p. 544.

<sup>1450</sup> Mars SG, *et al.*, “Every ‘Never’ I Said Came True”: Transitions from Opioid Pills to Heroin Injecting. *Int’l J. of Drug Policy*. 2014;25:257-266, at p. 264

<sup>1451</sup> Pielech, *et al.*, Receipt of Multiple Outpatient Prescriptions Is Associated With Increased Risk of Adverse Outcomes in Youth: Opioid Prescribing Trends, Individual Characteristics, and Outcomes from 2005-2016. *PAIN* 2020, published ahead of print. DOI:10.1097/j.pain.0000000000001812, at p. 2 (emphasis in original).

- xiv. The number of Americans aged 12 and older with past month heroin use, rose from 281,000 to 335,000 between 2011 and 2013, a significant increase from the 166,000 using heroin in 2002.<sup>1452</sup>
- xv. Jalal *et al.* (2018) also support the Gateway Effect, since those authors state: “Each drug’s mortality curve shows some variability. For example, the mortality rate from prescription opioids decreased slightly in 2012, whereas the mortality rates from heroin and synthetic opioids have been increasing rapidly. These trends may be related because several epidemic interventions may have reduced the impact of prescription opioids around 2010, including the reformulation of OxyContin in 2010, implementation of pain clinic laws and mandatory checking of Prescription Drug Monitoring Program data by prescribers, the reduction in the amount of opioids prescribed, and the rescheduling of hydrocodone compounds in 2014. Although these changes may have reduced the overdose deaths from prescription opioids, it is possible that they may have led some opioid-dependent persons to switch to illicit opioids such as heroin and fentanyl.”<sup>1453</sup>
- xvi. Another study put it this way: “The widespread availability of opioid analgesics outside sanctioned channels and, paradoxically, medical and regulatory attempts to curb this through monitoring and limiting prescribing, appear to be drawing a new generation into higher risk heroin injecting. Unlike those substances previously labeled ‘gateway drugs’, opioid pills seem to have a direct relationship with progression to heroin initiation.”<sup>1454</sup>
- xvii. In 2017, more than 28,000 deaths in the United States involved a synthetic opioid, primarily fentanyl, more deaths than from any other type of opioid.<sup>1455</sup>
- i. The epidemic of prescription opioid misuse, addiction, and overdose death beginning in the 1990s has been a significant factor contributing to the subsequent increase in heroin and fentanyl misuse, addiction, and overdose death. Further, the Pharmaceutical Opioid Industry knew that prescription opioids are a gateway to illicit opioids. In March 2011, Purdue’s “Hair Testing

<sup>1452</sup> McCarthy M. Illicit drug use in the US holds steady, but heroin use is on rise. *BMJ*. 2013;347(September):f5544. doi:10.1136/bmj.f5544, at p. 1.

<sup>1453</sup> Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018. doi:10.1126/science.aau1184, at pp. 1-2. (internal citations omitted)

<sup>1454</sup> Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. “Every ‘Never’ I Ever Said Came True”: Transitions from opioid pills to heroin injecting. *Int J Drug Policy*. 2014;25(2):257-266. doi:https://doi.org/10.1016/j.drugpo.2013.10.004, at p. 264.

<sup>1455</sup> Centers for Disease Control and Prevention. *Synthetic Opioid Overdose Data*, (Apr. 2, 2019) <https://www.cdc.gov/drugoverdose/data/fentanyl.html>.

Advisory Panel,” convened to help make the argument in favor of OxyContin’s “tamper-resistant formulation,” concluded that one of the “anticipated impacts of reformulation” was “reducing *OxyContin’s* role as a gateway drug” for recreational users.<sup>1456</sup>

- j. A lengthy and authoritative report issued in February 2022 by the U.S. Commission on Combating Synthetic Opioid Trafficking included the following significant conclusion: “The rise in illicit fentanyl and other synthetic opioid misuse and related deaths has its origins in the U.S. Food and Drug Administration’s approval of the prescription opioid painkiller OxyContin in 1995. Since then, the number of fatal drug overdoses has steadily climbed. *OxyContin and other prescription opioids were falsely marketed as an easy, nonaddictive fix for pain* without an appreciation of a patient’s other conditions, such as depression, trauma, and anxiety, which could drive the drugs’ misuse. *Prescription opioid dependence and addiction increased dramatically in the United States, and traffickers and other criminals exploited the opportunities presented.*”<sup>1457</sup>
- k. Increased access/exposure to prescription opioids contributed not only to increased heroin and illicit fentanyl death; it also contributed to increased non-opioid overdose deaths, including sedatives and stimulants. A 2020 study by Segel *et al.*, in examining the relationship between state-level opioid overdose death rates at the beginning of the opioid epidemic (1999-2004) and overdose death rates for opioids and other substances in later years (2005-2018), found the following: “our results suggest two characteristics of the opioid crisis: persistence and pervasiveness. In adjusted analysis, we found that for each additional opioid overdose death per 100,000 population at baseline, states had 23.5 more opioid deaths, 4.4 more heroin deaths, 8.0 more synthetic opioid deaths, 9.2 more sedative deaths, 3.3 more stimulant deaths, and 4.6 more cocaine deaths per population from 2005 to 2018.”<sup>1458</sup> In sum, “After adjusting for sociodemographic and state-level differences, baseline opioid overdose death rates in 1999-2004 were significantly associated with future opioid- and non-opioid-related overdose death rates.”<sup>1459</sup> The association reported by Segel *et al.* is likely to be causal because of the known phenomena of reinstatement (relapse) and cross-addiction, wherein patients addicted to prescription opioids are more susceptible to addiction to other drugs, especially when their drug of choice is not available.

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<sup>1456</sup> PPLP003370086 at 0106 (emphasis added).

<sup>1457</sup> United States of America Commission on Combating Synthetic Opioid Trafficking: Final Report. (Feb. 8, 2022) [https://www.rand.org/pubs/external\\_publications/EP68838.html](https://www.rand.org/pubs/external_publications/EP68838.html), at p. ix (emphasis added)

<sup>1458</sup> Segel JE, *et al.* Persistence and Pervasiveness: Early wave opioid overdose death rates associated with subsequent overdose death rates. *Public Health Reports*. 2020;00(0):1-7, at p. 1.

<sup>1459</sup> *Id.* at p. 3.



- i. Neuroscientists have shown that brain changes that occur after continuous heavy use of addictive substances can cause damage that does not resolve even after years of abstinence. One of the ways these irreversible changes can manifest is that the brain is primed to relapse to addictive physiology even after a single exposure to the addictive substance.<sup>1460</sup> This is called “reinstatement” by neurobiologists, and “relapse” by those who are addicted.
- ii. Reinstatement is not triggered solely by the substance that the individual was previously addicted to. Reinstatement can occur with any addictive substance because all drugs of abuse work on the same brain reward pathway.<sup>1461</sup> For example, animals repeatedly exposed to the addictive component of marijuana (tetrahydrocannabinol, or THC) and then not given THC for a period of time become addicted to morphine more quickly than animals not previously exposed to THC.<sup>1462</sup> This phenomenon is called cross-sensitization, or cross-addiction. Individuals who are addicted to opioids are consequently more susceptible to addiction to other drugs, including sedatives and stimulants.
- iii. I have written and published peer-reviewed literature describing the Gateway Effect on two occasions prior to my becoming an expert witness in the Opioid Litigation. In my 2016 book, *Drug Dealer MD*, I included a chapter with the title, “Prescription Drugs as the New Gateway to Addiction,” including a subchapter, “Vicodin: A Gateway Drug,” which recounted the example of a patient who transitioned from Vicodin to heroin after receiving the prescription hydrocodone drug for wisdom teeth removal. Similarly, in an article submitted for publication in 2017, and ultimately published in February 2018, I wrote: “Overprescribing of benzodiazepines may be fueling the use of illicit analogues, just as overprescribing of opioids has fueled increases in heroin and illicit fentanyl use.” These statements are consistent with the consensus in the field, that prescription opioids do indeed lead to transition to illicit opioids

**10. Increased supply of prescription opioids contributed substantially to more individuals, including newborns, becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect).**

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<sup>1460</sup> Steketee JD, Kalivas PW. Drug Wanting: Behavioral sensitization and relapse to drug-seeking behavior. *Pharmacol Rev.* 2011;63:348-365.

<sup>1461</sup> Nestler EJ, Is there a common molecular pathway for addiction? *Nature Neuroscience.* 2005;8(11):1445-1449.

<sup>1462</sup> Cadoni C, *et al.* Behavioral sensitization after repeated exposure to  $\Delta^9$ -tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology.* 2001;158:259-266, at p. 266.

- a. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased.
- b. Over the last 30 years, the liberal prescribing of opioids for chronic pain has created a “legacy” population of patients who have been on opioids for several years if not decades, and are now physically dependent on opioids, making it difficult to come off (The Dependence Effect).
- c. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for illness.<sup>1463</sup> Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.<sup>1464</sup> In the DSM-4, the edition prior to the DSM-5, “opioid use disorder” was called “opioid dependence.” The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor’s care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.
- d. By 2005, long-term opioid therapy was being prescribed to approximately 10 million Americans. “In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. Of these prescriptions, 65% were for short-term therapy (<3 weeks), but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.”<sup>1465</sup>

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<sup>1463</sup> Lembke, *et al.*, “Weighing the Risks,” fn. 5, above.

<sup>1464</sup> Delgado M, *et al.* National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naïve Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med.* 2018, at p. 1; *see also* Howard R, Fry B, Gunaseelan V, *et al.* Association of Opioid Prescribing with Opioid Consumption after Surgery in Michigan. *JAMA Surgery.* 2018, at p. E-6.

<sup>1465</sup> Volkow, *et al.*, “Misconceptions and Mitigation,” fn. 50, above, at p. 1253.

- e. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.
- f. Opioids cause neuroadaptation<sup>1466</sup> and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses.
- g. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.<sup>1467</sup>
- h. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.
- i. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,<sup>1468</sup> 71 (63%) continued high-dose opioids in the post-intervention period.<sup>1469</sup> In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.

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<sup>1466</sup> Koob, "Neurocircuitry", fn. 46, above, at p. 217.

<sup>1467</sup> Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; *see also* Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 77.

<sup>1468</sup> Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.

<sup>1469</sup> *Id.* at p. 114.

- ii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,<sup>1470</sup> only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote “Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general . . . .”<sup>1471</sup>
- i. The Pharmaceutical Opioid Industry consistently sought to downplay the importance of “dependence” on prescription opioids. As explained below, this effort included influencing the American Psychiatric Association’s change of the definitions of opioid-related disorders from the Diagnostic and Statistical Manual (DSM) IV to the DSM-5.
- j. On May 18, 2006, Purdue’s David Haddox received the “excellent news” from Sidney Scholl of Pinney Associates that “Chuck O’Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that ‘addiction’ will replace ‘dependence’ and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. . . . If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often.” Haddox wrote back, “This is really good news, Sid.”<sup>1472</sup>
- k. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe’s request for comments regarding the American Medical Association’s Report on Substance Abuse. Haddox wrote, “I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work...we are all fortunate that Charles O’Brien is the head of the substance use disorders section.”<sup>1473</sup>
- l. On November 6, 2008, Haddox wrote to Chuck O’Brien, “It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature that are applicable in the real (read: clinical) world.” Haddox went on to ask O’Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of \$2400 at O’Brien’s rate of \$600 per hour, “when it was anticipated

<sup>1470</sup> Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.

<sup>1471</sup> *Id.* at p. 1536.

<sup>1472</sup> PPLP004058443.

<sup>1473</sup> PPLPC031000425439.

that you would accompany us to the FDA Advisory Committee in March.” Haddox added, “Also, in the interest of public health and medicine, I don’t want to do anything to impair your ability to complete your DSM-V duties.” O’Brien wrote back on November 12, 2008, to “Dave, I would be very happy to do this but it would simplify my life with Penn if we could consider this activity an extension [of] my efforts of several months ago where I already signed a contract.” Haddox replied that he was “really pleased that you will be able to work with us on this.”<sup>1474</sup>

- m. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence “are inherent in pain management,” that is, “(1) Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use.” Haddox wrote to Lippe, “I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee].”<sup>1475</sup>
- n. Dr. O’Brien’s consulting and financial relationship with Purdue goes back to at least 2003.<sup>1476</sup> Through 2006, Dr. O’Brien appeared as an expert witness for Purdue in at least 9 cases in the federal courts of Florida, Missouri, Ohio, Texas, Georgia and Illinois and Texas state court<sup>1477</sup> providing opinions that plaintiffs were not addicted; not injured by dependence, which was described as an “expected consequence” of taking OxyContin and easily resolved by tapering.<sup>1478</sup> In the *Savant v. Purdue* case in 2005, Dr. O’Brien’s report stated that he was compensated at the rate of \$550 per hour.<sup>1479</sup> O’Brien signed a consulting agreement with Purdue, effective from April 2008-April 2013,<sup>1480</sup> essentially contemporaneous with his tenure as Chair of the DSM-5 Substance

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<sup>1474</sup> PPLPC018000252189 at -2190-2191.

<sup>1475</sup> PPLPC018000201219 at -1219-1222.

<sup>1476</sup> Dr. O’Brien testified that since 1969, he has been a paid consultant to numerous pharmaceutical/opioid manufacturers including McNeil, Janssen, Johnson & Johnson, Cephalon, Purdue and others. O’Brien also testified that he “helped them [McNeil] decide to purchase Tramadol from a German company and help them get that started.” *Timmons v Purdue Pharma* (2005) Deposition of Charles P. O’Brien, produced at PKY183320282 at -0393-0394.

<sup>1477</sup> *Timmons v Purdue Pharma et al.* No. 8:04-CV-1479-T-26MAP (M.D. Fla., 2005) produced at PKY183320282; *Savant v Purdue Pharma et al.*, No. 04-394-DRH, 2005 WL 6503987 (S.D. Ill. 2005); *Taylor v Purdue Pharma et al.*, No. 504-CV-197, 2005 WL 3308504 (M.D. Ga. 2005); *McKnight v Purdue Pharma et al.*, No. 9:04 Civ-116, 2005 WL 5794391 (E.D.Tex. 2005); *Harris v Purdue Pharma et al.*, No. C-1-01-428, 2004 WL 4012101 (S.D. Ohio 2004); *Branch v Purdue Pharma et al.* No. LR 1696-3, 2004 WL 3752789 (Tex. Dist. Richmond Civil); *Campbell v Purdue Pharma et al.*, No. 1:02CV00163TCM, 2004 WL 6057307 (E.D. Mo. 2004); *Labzda v Purdue Pharma et al.*, No. 01-8726-CIV-FERGUSONSNOW, 2003 WL 26100920 (S.D. Fla. 2003); *Williams v Purdue Pharma et al.*, No. 4:04CV02407 (S.D. Tex. 2006), produced at PKY182921037

<sup>1478</sup> *Harris*, 2004 WL 4012101, at \*5.

<sup>1479</sup> *Savant*, 2005 WL 6503987, at \*9.

<sup>1480</sup> PPLP003478540

Abuse working group, from 2007-2013.<sup>1481</sup> Remarkably, in 2013, O'Brien disclosed no financial relationship to Purdue or any other party as a co-author and Chair of the group that published the rationale for the changes to the new DSM-5 section on substance abuse.<sup>1482</sup>

- o. This sequence of events indicates that Purdue's consultant, O'Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-5 definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue and other opioid manufacturers to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena. Further, by excluding the criteria of tolerance and withdrawal, and by completely removing dependence from the diagnostic criteria, the DSM-5 raised the threshold for diagnosing OUD in this vulnerable population, consisting of approximately 25% of long-term opioid users who progressed to OUD.<sup>1483</sup> As a result of making it more difficult to diagnose OUD, some of these patients were denied the benefits of timely, evidence-based treatment of their conditions.
- p. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.
- q. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at significant risk to continue them beyond the time of injury, *i.e.* to become dependent on them.
  - i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naïve patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By

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<sup>1481</sup> Hasin DS, O'Brien CP *et al.* DSM-5 Criteria for Substance Use Disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834-851. at p.2, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/pdf/nihms515995.pdf>, at p. 2.

<sup>1482</sup> *Id.* at pp. 1 and 12.

<sup>1483</sup> Vowles, "Rates of Opioid Misuse", fn. 1224, above, discussed above at §C.8.b.



comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, “New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness.”<sup>1484</sup> The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.

- ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is “common,” and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, “This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing.”<sup>1485</sup>
- iii. A 2020 retrospective cohort study of 259,115 opioid naïve adult patients undergoing endocrine surgery found the rate of new persistent opioid use [*i.e.*, receipt of 1 or more opioid prescriptions 90-180 days postop with no intervening procedures] was 7.4% but that “[i]mportantly, the risk for persistent opioid use increased with higher doses of total amount of opioids prescribed.”<sup>1486</sup>
- iv. A 2022 study mentioned previously found 29.9% of patients transitioned from acute opioid use to chronic opioid use. Risk factors included higher MME, higher tablet count and longer prescription duration in the initial opioid prescription.<sup>1487</sup> The study demonstrated a “dose-dependent relationship between [the number of] tablets prescribed and chronic opioid use risk.”<sup>1488</sup> These findings support my experience that the more times per day people can dose themselves, especially with short-acting opioids, the more likely they are to develop opioid use disorder.

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<sup>1484</sup> Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in U.S. adults. *JAMA Surg.* 2017., at p. 1.

<sup>1485</sup> Delgado, *et al.*, “National Variation,” fn. 1464, above, at p. 1

<sup>1486</sup> Kuo JH, *et al.* Use and Misuse of Opioids after Endocrine Surgery Operations. *Annals of Surgery.* 2020:1-6, at p. 1.

<sup>1487</sup> Johnson, “Prescription quantity and duration”, fn. 1307, above, at p. 1.

<sup>1488</sup> *Id.*, at p. 10.

- v. Numerous other studies have been published showing persistent opioid use 3-12 months after even minor surgeries in opioid naïve patients: (10%<sup>1489</sup>; 10%<sup>1490</sup>; 5%<sup>1491</sup>; 13%<sup>1492</sup>; 13%<sup>1493</sup>; 8%<sup>1494</sup>; 10%-13%<sup>1495</sup>)
- r. Conversely, the fewer opioids prescribed in the weeks and months following surgery, the less likely patients are to become persistent opioid users.<sup>1496</sup> When opioids are restricted, patients do not tend to experience more pain, less satisfaction, or call in more frequently for refills.<sup>1497</sup>
- s. A 2020 NASEM Report addresses the role of opioid prescribing for acute pain, including surgical and other contexts, as a contributing factor to the epidemic of abuse, overdose and mortality.<sup>1498</sup> The Report confirms the increasing awareness that opioids are overprescribed even for acute pain, and that an important subset of acute pain patients go on to long-term use of prescription opioids and the risks that accompany such use.<sup>1499</sup>

<sup>1489</sup> Marcusa DP *et al.* Prescription Opioid Abuse among Opioid-Naïve Women Undergoing Immediate Breast Reconstruction. *Plast Reconstr Surg.* 2017 Dec;140(6):1081-1090. doi: 10.1097/PRS.0000000000003832, at p. 1081.

<sup>1490</sup> Lee JS *et al.* New Persistent Opioid Use Among Patients with Cancer after Curative-Intent Surgery. *J Clin Oncol.* 2017 Dec 20;35(36):4042-4049. doi: 10.1200/JCO.2017.74.1363, at p. 4042.

<sup>1491</sup> Harbaugh, *et al.*, “Persistent Opioid Use”, fn. 1437, above, at p. 1.

<sup>1492</sup> Deyo RA *et al.* Use of Prescription Opioids Before and After an Operation for Chronic Pain (lumber fusion surgery). *Pain.* 2018 Jun;159(6):1147-1154. doi: 10.1097/j.pain.0000000000001202, at p. 5.

<sup>1493</sup> Johnson SP *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients Following Common Hand Surgery Procedures. *J Hand Surg Am.* 2016 Oct;41(10):947-957.e3. doi: 10.1016/j.jhsa.2016.07.113, at p. 947.

<sup>1494</sup> Goesling J *et al.* Trends and Predictors of Opioid Use After Total Knee and Total Hip Arthroplasty. *Pain.* 2016 Jun;157(6):1259-65. doi: 10.1097/j.pain.0000000000000516, at p. 1259.

<sup>1495</sup> Cook DJ *et al.* Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: a database analysis of 69,368 patients. *J. Arthroplasty.* 2019; 34: 638-644, at p. 638.

<sup>1496</sup> Brummett, “New Persistent Opioid Use”, fn. 1484, above; Gil JA, *et al.* Risk of Prolonged Opioid Use Among Opioid-Naïve Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med* 2019; 47(5): 1043-1050, at p. 1049; Larach DB, Sahara MJ, *et al.* Patient Factors Associated with Opioid Consumption in the Month Following Major Surgery. *Ann Surg.* 2019; 1-9, at p. 1.

<sup>1497</sup> Bateman BT, Cole NM, *et al.* Patterns of opioid prescription and use after cesarean delivery. *Obstet Gyn.* 2017; 130(1): 1-17, at p. 3; Howard R, *et al.* Reduction in opioid prescribing through evidence-based prescribing guidelines. *JAMA Surg* 2018; 153(3): 285-287, at p. 287; Lee JS, Hu HM, Brummett CM, *et al.* Postoperative Opioid Prescribing and the Pain Scores on Hospital Consumer Assessment of Healthcare Providers and Systems Survey. *JAMA.* 2017;317(19):2013–2015, at p. 2014; Sekhri S, Arora NS, *et al.* Probability of opioid prescription refilling after surgery: does initial prescription dose matter? *Ann Surg.* 2018; 268(2): 271-276, at p. 275.

<sup>1498</sup> National Academies of Sciences, Engineering, and Medicine (NASEM 2020). 2020. *Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence.* Washington, DC: The National Academies Press..<https://www.nap.edu/catalog/25555/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence>

<sup>1499</sup> *Id.* at p. 1. A further recent publication adds to this evidence: among women who took prescription opioids for acute pain after childbirth, there was an increased risk of Serious Opioid-Related Events (a composite consisting of persistent opioid use, opioid use disorder diagnosis, methadone or buprenorphine prescription, opioid overdose diagnosis, and opioid-related death) compared with women who did not take opioids after childbirth, and the risk increased with more post-partum opioid prescriptions. Osmundson SS, *et al.*, Opioid prescribing after childbirth and

- t. Just as increased exposure has been the cause of increased consumption and risk,<sup>1500</sup> decreasing exposure decreases opioid consumption and risk. When doctors initiate fewer opioids, patients consume fewer opioids, without increases in pain. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment, while at the same time reducing the risk of diversion of unused pills to unauthorized users. Recent studies in a wide range of medical conditions have consistently demonstrated that patients' experience of pain is not increased when opioids are reduced or eliminated from treatment protocols. Examples of research are summarized below.
  - i. In a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients "need very little, if any, post-operative opioids....Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction."<sup>1501</sup>
  - ii. A case-control cohort study of 1,231 patients undergoing gynecologic oncology surgery, implemented an "ultrarestrictive opioid prescription protocol" (UROPP), resulting in a significant decrease in the number of opioids dispensed during the entire perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.<sup>1502</sup>
  - iii. The authors write, "For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation ( $P < .001$ ). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation ( $P < .001$ ). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naïve patients ( $P < .001$ )."<sup>1503</sup>
  - iv. "The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104

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risk for serious opioid-related events: a cohort study. *Annals of Internal Medicine* 2020; doi:107326/M19-3805, at p. 2.

<sup>1500</sup> Howard, *et al.*, "Association of Opioid Prescribing," fn. 1464, above, at p. E6.

<sup>1501</sup> Shindo M, Lim J, Leon E, Moneta L, Li R, Quintinalla-Diek L. Opioid Prescribing Practice and Needs in Thyroid and Parathyroid Surgery. *JAMA Otolaryngology - Head and Neck Surgery*. 2018, at p. 1102.

<sup>1502</sup> Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. *JAMA Netw Open*. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.

<sup>1503</sup> *Id.* at p. 1.

patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group;  $P = .99$ ), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group;  $P = .06$ ), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group;  $P = .15$ ).<sup>1504</sup>

- v. Similarly, non-opioids have been found equivalent to opioids for relief of pain treated in emergency departments. “For adult ED [Emergency Department] patients with acute extremity pain, there were no clinically important differences in pain reduction at 2 hours with ibuprofen and acetaminophen or 3 different opioid and acetaminophen combination analgesics.”<sup>1505</sup> Based on data from 2006-2010, opioids were prescribed for 18.7% of ED discharges; yet “[t]he findings support the inference that there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for the treatment of acute extremity pain in the ED.”<sup>1506</sup>
- u. In most cases, opioid dependent patients require a protracted medically supervised taper to lower their doses. I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. *See* discussion of the “BRAVO Protocol” and my recent publication on patient-centered tapering, below. Studies show that pain in the majority of patents *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.
- v. It is inhumane to abruptly discontinue opioids in patients who have become dependent through a medical prescription.<sup>1507</sup> The preferred approach is a slow and compassionate taper<sup>1508</sup> when risks outweigh the benefits.
- w. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had

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<sup>1504</sup> *Id.* at pp. 1-2.

<sup>1505</sup> Chang AK, *et al.* Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. *JAMA*. 2017;318(17):1661–1667. doi:10.1001/jama.2017.16190, at p.1661.

<sup>1506</sup> *Id.*

<sup>1507</sup> United States Department of Health and Human Services. *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesics*. (Oct. 2019); [https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage\\_Reduction\\_Discontinuation.pdf](https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf).

<sup>1508</sup> *Id.* at p. 3, opioid tapering flowchart based on Oregon Pain Guidance BRAVO protocol.

significant improvements in pain-related measures including numeric pain scores and functionality.<sup>1509</sup>

- x. A meta-analysis of opioid legacy patients (patients on long-term opioid therapy as a “legacy” of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long-term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).<sup>1510</sup> The authors repeatedly note the need for more research and better quality evidence. Nonetheless, the authors concluded, “this systematic review suggests that pain, function and quality of life may improve during and after opioid dose reduction.”<sup>1511</sup>
- y. In a study by Sullivan *et al.*, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).<sup>1512</sup> The authors write, “It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0-10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction.”<sup>1513</sup>
- z. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg (P = .002). Of

<sup>1509</sup> Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. *Pain Med* (United States). 2016. doi:10.1093/pm/pnv079, at p. 1676.

<sup>1510</sup> Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. *Ann Intern Med*. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.

<sup>1511</sup> *Id.* at p. 186.

<sup>1512</sup> Sullivan MD, Turner JA, DiLodovico C, D’Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain*. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.

<sup>1513</sup> *Id.* at p. 318.

note, neither pain intensity ( $P = .29$ ) nor pain interference ( $P = .44$ ) increased with opioid reduction.<sup>1514</sup>

- aa. Many patients on chronic opioid therapy are reluctant to taper. In addition, some physicians and authors question whether tapering is necessary if the patient is stable and adherent to their current dose. Yet it is well established that patients on high doses of opioids are at increased risk for a variety of side effects, serious morbidities, and death.<sup>1515</sup> Quality of life may be adversely affected, despite the fact that the patient perceives benefit in terms of pain relief. Indeed, as above, data show that in addition to reducing opioid-related risk, pain can improve when patients lower their opioids, which is evidence in and of itself that opioids do not work for chronic pain for those patients.
- bb. A newborn is born dependent on opioids as a result of being exposed to opioids *in utero*. According to DSM-5 criteria, the opioid dependent newborn is not “addicted,” because addiction requires the manifestations of certain pathological and maladaptive behaviors in conjunction with opioid use. The newborn is the passive recipient of opioids due to the mother’s exposure.
  - i. The rate of admission to neonatal intensive care units (“NICU”) for neonatal abstinence syndrome (“NAS”), a drug-withdrawal syndrome that occurs after in utero exposure to opioids, increased from 7 cases per 1000 admissions to 27 cases per 1000 admissions between 2004 and 2013.<sup>1516</sup>
  - ii. Tolia reported that “the median length of stay increased from 13 days to 19 days ( $P < 0.001$  for both trends). The total percentage of NICU [neonatal intensive care unit] days nationwide that were attributed to the neonatal abstinence syndrome increased from 0.6% to 4.0% ( $P < 0.001$  for trend), with eight centers reporting that more than 20% of all NICU days were attributed to the care of these infants in 2013.”<sup>1517</sup>
  - iii. This approximate quadrupling of the rate of NAS is directly attributable to the epidemic of opioid use disorder that began with promotion of

<sup>1514</sup> Darnall BD, Ziadni MS, Stieg RL, Mackey IG, Kao MC, Flood P. Patient-centered prescription opioid tapering in community outpatients with chronic pain. *JAMA Intern Med.* 2018. doi:10.1001/jamainternmed.2017.8709, at p. 708.

<sup>1515</sup> Gomes T, Mamdani MM, Dhalla Ia, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691. doi:10.1001/archinternmed.2011.117, at p. 686; *see also* Lembke *et al.*, “Weighing The Risks,” fn. 5, above, at p. 982; Edlund *et al.*, “Role of Opioid Prescription,” fn. 75, above, at p. 7; Chou *et al.*, “Effectiveness and Risks,” fn. 414, above, at p. ES-1.

<sup>1516</sup> Tolia VN, Patrick SW, Bennett MM, *et al.* Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *Obstet Gynecol Surv.* 2015. doi:10.1097/OGX.0000000000000243, at p. 2118.

<sup>1517</sup> *Id.* at p. 2118.



prescription opioids and continues to the present, accompanied by use of illicit opioid drugs.

- cc. Defendants' promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own clinical experience, and patients' own accounts.<sup>1518</sup> This messaging improperly contributed to physicians' false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (*See* Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (*see* Appendix I) are inconsistent with the medical evidence that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

**11. Increased supply of prescription opioids contributed substantially to diversion of prescription opioids to individuals for whom they had not been prescribed (The Tsunami Effect).**

- a. As stated in the 2013 CDC Report: "Almost all prescription drugs involved in abuse come from prescriptions originally. However, once they are prescribed and dispensed, prescription drugs are frequently diverted to people using them without prescriptions. There are instances where pharmacies are dispensing large quantities of opioids as part of an illegal distribution scheme as well as pharmacists who fail to meet their obligation to determine that a prescription was issued for a legitimate medical purpose."<sup>1519</sup>
- b. This quote highlights the large role that diversion of prescription opioids has played in the current epidemic. In addition to people getting addicted to and being harmed by opioids prescribed directly to them, millions have been harmed through diversion of prescription opioids to unauthorized sources, from teenagers experimenting to people already addicted to opioids gaining easier access through the illicit market.
- c. An efficient distributor supply chain enabled opioid manufacturers to make prescription opioids available on a mass scale to large numbers of people in rural and remote settings, as well as urban and suburban settings, expanding both the licit and illicit drug market, and setting this opioid epidemic apart from prior epidemics and other drug epidemics. The sheer scale of access to opioids made possible through the distribution and supply chain, led

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<sup>1518</sup> Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff.* 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

<sup>1519</sup> United States Department of Health and Human Services. Addressing Prescription Drug Abuse in the United States. :1-36, at p. 16. *See* [https://www.cdc.gov/drugoverdose/pdf/hhs\\_prescription\\_drug\\_abuse\\_report\\_09.2013.pdf](https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf).

individuals who otherwise would never have been exposed, to use and subsequently be killed or harmed by opioids.<sup>1520</sup>

- d. As stated in a recent NASEM report, “the increase in the availability of drugs and both the long-term and increasing vulnerability of these population groups combined to create and fuel the rising trend in drug poisoning deaths. The country’s drug overdose crisis represents a ‘perfect storm’ of the flooding of the market with highly addictive yet deadly substances and underlying U.S. demand for and vulnerability to substances that temporarily numb both physical and mental pain.”<sup>1521</sup>
- e. It is important to recognize that although many of the communities hit hardest by the opioid epidemic were already struggling with serious social and economic problems, the sudden availability of and easy access to opioids, initially in prescription pill form, contributed to the economic and social devastation of many towns across America.<sup>1522</sup> Economic downturn and the efflux of manufacturing jobs in towns across America in the last thirty years, have contributed to so-called “deaths of despair” – early mortality in middle aged non-Hispanic whites due primarily to drug overdose.<sup>1523</sup> In a March 2020 interview, co-author Angus Deaton further stated that “the economic and social distress has just been unwinding for a really, really long time. *And then the opioids threw fuel on that fire and turned it into a full raging epidemic.*”<sup>1524</sup> Nonetheless, economic disadvantage contributes only 10-20% of mortality risk attributable to opioids, whereas the larger share of risk is due to supply of opioids in a given geographic region.<sup>1525</sup>
- f. ARCOS data on opioid prescribing show a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales at the county level.<sup>1526</sup> These data demonstrate a clear and convincing relationship between opioid dispensing and opioid related harm.<sup>1527</sup>
- g. Khan *et al.*, writing in *JAMA Internal Medicine* in 2019, show that an opioid prescription to one family member increases the risk of opioid overdose death to others in the same family, even though they do not have an opioid

<sup>1520</sup> See also §C.2.j, above, re likely extent of diversion of prescription opioids.

<sup>1521</sup> NASEM 2021, fn. 92, above, at p. 7-19.

<sup>1522</sup> Ruhm CJ. Deaths of Despair or Drug Problems? NBER Working Paper No. 24188, NBER Program(s):Health Care, Health Economics, Public Economics, *National Bureau of Economic Research, Inc.* (2017).

<sup>1523</sup> Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci.* 2015. doi:10.1073/pnas.1518393112, at p. 15081.

<sup>1524</sup> “Deaths of Despair – Case and Deaton Full”. <https://www.youtube.com/watch?v=jiPBEota8DI> (posted March 17, 2020).

<sup>1525</sup> Ruhm, *et al.*, “Deaths of Despair,” fn. 1522, above.

<sup>1526</sup> Ghertner R. U.S. County Prevalence of Retail Prescription Opioid Sales and Opioid-Related Hospitalizations from 2011 to 2014. *Drug and Alcohol Dependence* 194 (2019):330–335, at p. 330.

<sup>1527</sup> *Id.* at p. 333.

prescription. This study identifies 2,303 individuals who experienced opioid overdose and 9,212 matched control individuals, and shows that any prior opioid dispensing to family members was associated with overdose (odds ratio [OR], 2.89 [95% CI, 2.59-3.23]) in other family members. Risk of overdose increased in a dose-response fashion: Odds of overdose (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).<sup>1528</sup>

- h. A 2021 study examining parents prescribed opioids for medical conditions found that their adolescent children are more likely to be prescribed opioids as well as misuse prescription opioids. The study found that “controlling for other factors, parental medical prescription opioid use was associated with adolescent prescription opioid medical use (adjusted odds ratio [aOR] 1.28; 95% CI, 1.06-1.53) and misuse (aOR, 1.53; 95% CI, 1.07-2.25), whereas parental misuse was not.”<sup>1529</sup> The authors found that “the association of parental medical prescription opioid use with adolescent prescription opioid misuse suggests that role modeling and availability of parents’ opioid medications in the household are significant familial risk factors for prescription opioid misuse among young people, although adolescents also misuse their own prescription opioid medications and prescriptions opioids from nonfamilial sources.”<sup>1530</sup>
- i. A study of US 12<sup>th</sup> grade adolescents found that students attending schools with the highest rates of medical use of prescription opioids had a 57% increased odds of prescription opioid misuse, compared with schools that had no medical use of prescription opioids.<sup>1531</sup> “The robust association between school-level medical use of prescription opioids and POM [prescription opioid misuse] is consistent with evidence showing the largest sources of prescription opioids among adolescents are peers and leftover medication.”<sup>1532</sup> The authors state that this association has weakened in recent years, which may be due to the impact of efforts to reduce prescription opioid misuse, or because adolescents “are turning to more readily available substances (*e.g.*, marijuana, heroin) as prescription opioids become less available.”<sup>1533</sup>
- j. The recent NASEM report on guidelines for opioid use for acute pain (NASEM 2020), referenced above, further states that “Opioids pose risks not only to the patients for whom they are prescribed, but also to family members

<sup>1528</sup> Khan NF, Bateman BT, *et al.* Association of Opioid Overdose with Opioid Prescription to Family Members. *JAMA Intern Med.* doi:10.1001/jamainternmed.2019.1064, at p. E3.

<sup>1529</sup> Griesler PC, *et al.* Assessment of prescription opioid medical use and misuse among parents and their adolescent offspring in the US. *JAMA Network Open.* 021;4(1):1-16, at p. 1.

<sup>1530</sup> *Id.* at p. 11.

<sup>1531</sup> McCabe SE, *et al.* Medical use and misuse of prescription opioids in US 12<sup>th</sup> grade youth: School-level correlates. *Pediatrics.* 2020;146(4):1-13, at p. 1.

<sup>1532</sup> *Id.* at p. 8.

<sup>1533</sup> *Id.* at p. 9.

and to the community. Unused opioid pills from opioid prescriptions can be diverted to family members and friends (Bicket *et al.*, 2019; Hill *et al.*, 2017; Howard *et al.*, 2019; Thiels *et al.*, 2017). These unused pills, which often are not disposed of properly, may be used by the patient for indications other than those for which they were prescribed (*e.g.*, as a sleep aid), or they may be used by someone other than the patient (Bicket *et al.*, 2017; Jones *et al.*, 2014). Individuals with opioid use disorder commonly report that they started by misusing prescription opioids (Ali *et al.*, 2019; Becker *et al.*, 2008; Cicero *et al.*, 2014; NASEM, 2019). Furthermore, there is an association between the size of a patient's opioid prescription and the likelihood of an opioid overdose among the patient's family members (Khan *et al.*, 2019). This association is present in children and adolescents as well as in adults (Khan *et al.*, 2019). Among individuals who misuse prescription opioids, the most common source of opioids was pills from family members and friends. Among individuals who use heroin, the majority (66%) previously misused prescription opioids (Cicero *et al.*, 2014). *Thus, opioid overprescribing, that is, prescribing more opioids than are necessary to control a patient's acute pain, is a factor contributing to the public health epidemic of opioid overdoses.*"<sup>1534</sup>

- k. Opioid overprescribing after surgery is a significant contributor to the Tsunami Effect. A recent study reported that 83% of US patients who reported no pain after operation were discharged on opioids compared with 8.7% of non-US patients ( $p < 0.001$ ).<sup>1535</sup> After discharge, the number of opioid prescription refills was substantially higher among US patients compared with non-US patients (7.1% vs 0.1%;  $p < 0.001$ ).<sup>1536</sup> US patients were also prescribed more pills in higher doses than their non-US counterparts. The mean adjusted OME [oral morphine equivalent] and number of pills for US patients increased from 156.1 OME and 20.6 pills in US patients without pain, to 213.4 OME and 27.1 pills in US patients with severe pain, compared to non-US prescribing of 9.8 OME and 1.4 pills in non-US patients without pain and 26.8 OME and 4.5 pills in non-US patients with severe pain.<sup>1537</sup> The authors state that "The large quantity of unused pills increases the risk of opioid misuse and diversion to the community at large."<sup>1538</sup> The frequent and completely unnecessary prescription of powerful and addictive drugs to patients who are not experiencing any degree of pain is emblematic of the extent to which the Defendants' false messages of prescription opioid safety, and their ubiquitous distribution, have permeated the medical profession and continue to exert their harmful influence.

<sup>1534</sup> NASEM 2020, fn. 1498, above, at pp. 15-16 (emphasis added).

<sup>1535</sup> El Moheb M, *et al.* Pain or No Pain, We Will Give You Opioids: Relationship between number of opioid pills prescribed and severity of pain after operation in U.S. vs non-U.S. patients. *J Am Coll Surg.* 2020;231(6):639-648, at p. 642-644.

<sup>1536</sup> *Id.* at p. 642.

<sup>1537</sup> *Id.* at p. 643.

<sup>1538</sup> *Id.* at p. 646.

1. Finally, an objective observer would have appreciated that the number of opioid pills being shipped to pharmacies all over the United States was far in excess of medical need. Annual Production Quotas (APQs) that were approved by the DEA, despite FDA recommendations for lower amounts, were based on unsupported Industry claims of market demand, without consideration of the obvious concern that the requested APQs included substantial diversion that contributed to the prescription opioid epidemic. While the DEA bears some responsibility for routinely accepting sales figures and unsupported claims of increased demands as a proxy for legitimate needs,<sup>1539</sup> the Industry itself bears primary responsibility for submitting requests for APQs that “were clearly excessive from 2010-2016.”<sup>1540</sup>

**12. The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. “Epidemic,” defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990’s and continuing to the present day.**

- a. The Stanford-*Lancet* Commission described the evolution and continuing threat resulting from the overprescribing and oversupply of prescription opioids, stating that “[t]he opioid crisis has shown that in the absence of adequate supply control over addictive drugs, damage to human health and wellbeing is unavoidable.”<sup>1541</sup> Further, the harms of the opioid epidemic are urgent and ongoing: “Large numbers of US and Canadian people are still becoming addicted to prescription opioids each year, and most of those who die from heroin and fentanyl overdoses are previous or current users of prescription opioids.”<sup>1542</sup> The Commission’s opioid crisis model estimates that, in the absence of any intervention, an additional 1,220,000 fatal opioid overdoses will occur in the US between 2020 and 2029.<sup>1543</sup>
- b. The societal effects of this opioid epidemic are worse than the societal effects of other drug epidemics, because of the accelerated devastation to individuals and communities, including (i) high rates of addiction and death in young people in the prime of their lives; (ii) high rates of pregnant women being exposed to opioids and giving birth to babies dependent on opioids, who in turn suffer long-term cognitive consequences;<sup>1544</sup> (iii) the tragic disruption to

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<sup>1539</sup> State of West Virginia Office of the Attorney General, “DEA’s Failure to Combat Diversion Cost Lives: results from the West Virginia Attorney General’s Investigation into the DEA’s catastrophic failure to manage the National Drug Quota System from 2010-2016, (June 4, 2020), at p. 29

<sup>1540</sup> *Id.* at p. ES-4.

<sup>1541</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 5.

<sup>1542</sup> *Id.*

<sup>1543</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 12.

<sup>1544</sup> Yeoh SJ, *et al.* Cognitive and motor outcomes of children with prenatal opioid exposure: a systemic review and meta-analysis. *JAMA Network Open.* 2019; 2(7): 1-14, at pp. 1-2.

families and communities due to loss of parental caregivers,<sup>1545</sup> requiring substantial resources for foster care; and (iv) exodus from the work force as a result of opioid dependence and addiction.<sup>1546</sup>

i. Long-term effects of Prenatal Opioid Exposure (“POE”)

- A. In a recent *JAMA* meta-analysis, the authors reported statistically significant cognitive and motor deficits among children exposed to prenatal opioids compared to unexposed children, from birth through age 6; deficits found among children from age 7-18 were no longer statistically significant.<sup>1547</sup> The authors stated, “The cause and association of this with POE or other factors (*e.g.*, withdrawal treatment) are uncertain but suggest that POE necessitates long-term support and intervention.”<sup>1548</sup> It should be noted that, to the extent that “withdrawal treatment” may be a cause of the observed deficits, such treatment itself would not have been required if not for the POE that precipitated the withdrawal and accompanying need for treatment. Further, “children with POE are 3 times more likely to have severe intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria . . . . Poor neurodevelopmental outcomes in children with POE, even from an early age, is not novel information. However, our data appear to indicate that neurodevelopment did not improve after preschool and worsened by school age.”<sup>1549</sup>
- B. Similar results were reported in a study of the academic testing of Australian children who had been diagnosed with NAS at birth. Test scores of NAS children were compared to those of matched controls and the general population, at Grades 3, 5, 7, and 9, which correspond to ages 8-9, 10-11, 12-13, and 14-15, respectively. The authors reported, “Our results show that a diagnosis of NAS is associated with poorer performance in standardized and compulsory curriculum-based tests from as early as 8 or 9 years of age in grade 3 of school when

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<sup>1545</sup> Radel L, Baldwin M, *et al.* Substance use, the opioid epidemic, and the child welfare system: key findings from a mixed methods study. *ASPE Research Brief*. (March 7, 2018)

<sup>1546</sup> Franklin GM, *et al.* Early opioid prescription and subsequent disability among workers with back injuries. *Spine*. 2008; 33(2): 199-204; *see also* Anora M. Gaudiano, *How the opioid epidemic is exacerbating a US labor-market shortage*. MarketWatch, June 29, 2018. <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

<sup>1547</sup> Yeoh, “Cognitive and Motor Outcomes”, fn. 1544, above.

<sup>1548</sup> *Id.* at p. 2.

<sup>1549</sup> *Id.* at pp. 8-9.



compared with other NSW [New South Wales] children, including those who were matched for gender, gestation, and socioeconomic status. Indeed, by the first year of high school, children with NAS performed even more poorly than other children in grade 5 who were, on average, 2 years younger. By grade 7, 44% of children with NAS had failed to meet NMS [National Minimum Standards] in  $\geq 1$  domain of testing.”<sup>1550</sup>

- C. While noting that the cause for these effects is “uncertain,” the authors cited known biological mechanisms that could reasonably explain the deficits: “NAS is caused by transplacental exposure to drugs of addiction or dependency that interfere with brain function and development. Opioids impair adult brain function and cognitive skills even after only a few days of use, and their effects on the developing brain are subtle but long-lasting and include alterations to neuronal apoptosis, dendritic morphogenesis, and neurotransmitter homeostasis.”<sup>1551</sup> Further, the risk of failure to meet NMS (OR=2.5) was greater for NAS than for any other risk factor investigated.<sup>1552</sup>
- D. The consistency of results from the Yeoh and Oei studies provides support for the conclusion that NAS contributes substantially to persistent developmental deficits. “This finding is of great concern because school failure increases the risk of myriad poor adult outcomes, including depression in women, criminal activity, and drug use. We showed that children with NAS performed more poorly in all 5 test domains, including reading or literacy skills, 1 of the most important predictors of school success. Children who cannot read at expected levels by grade 3 are less likely to enroll in college or graduate high school. In the United Kingdom, two-thirds of prisoners have a reading age <11 years. Furthermore, test results in children with NAS worsened as they entered high school.”<sup>1553</sup>
- E. A recent study found developmental delays among infants exposed to opioids in utero, even where the newborns displayed no overt symptoms of NAS. The authors reported, “Compared to infants with no detected exposures the

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<sup>1550</sup> Oei JL, *et al.* Neonatal Abstinence Syndrome and High School Performance. *Pediatrics*. 2017;139(2):e20162651, at p. 7.

<sup>1551</sup> *Id.*

<sup>1552</sup> *Id.*

<sup>1553</sup> *Id.*

diagnosis of developmental delay was highest among infants with NAS (7.6% versus 28.3%). However, the diagnosis was still twice as likely among opioid exposed infants without NAS (7.6% versus 15.6%).”<sup>1554</sup>

- ii. Loss of Parental Caregivers and Impacts on Foster Care: A 2018 study of the relationship between drug use and foster care reported, “Higher rates of overdose deaths and drug hospitalizations correspond with higher child welfare caseload rates. We estimate that in the average county nationwide, a 10 percent increase in the overdose death rate corresponded to a 4.4 percent increase in the foster care entry rate. Similarly, a 10 percent increase in the average county’s drug-related hospitalization rate corresponded to a 2.9 percent increase in its foster care entry rate.”<sup>1555</sup> While the increased rates of overdose deaths are not exclusively linked to opioids, data cited previously support the significantly greater share of drug mortality attributable to opioids than to other drugs.<sup>1556</sup>
- iii. Exodus from the workforce: It is well-known that widespread distribution and use of opioids has had a significant adverse effect on the availability of workers, both due to increased mortality and the myriad problems associated with opioid use. According to a recent analysis, “The opioid epidemic is preventing a huge portion of the population that is sidelined from joining the labor force because labor intensive jobs are also the ones that require workers who can pass drug tests.”<sup>1557</sup> The opioid epidemic is responsible for this detrimental impact. Franklin (2008) found that “receipt of opioids for more than 7 days (odds ratio 2.2; 95% confidence interval, 1.5-3.1) and receipt of more than 1 opioid prescription were associated significantly with work disability at 1 year.” Another study of long-term opioid use and opioid use disorder among construction workers found that “workers prescribed long-term opioids in any calendar quarter had a nearly 10-fold odds of developing an OUD.”<sup>1558</sup> An additional study of labor

<sup>1554</sup> Hall ES *et al.* Developmental disorders and medical complications among infants with subclinical intrauterine opioid exposures. *Population Health Management*. 2019;22;19-24, at p. 21.

<sup>1555</sup> Radel, “Child Welfare System”, fn. 1545, above, at pp. 2-3.

<sup>1556</sup> See, e.g., Centers for Disease Control and Prevention, *Opioid Overdose*, <https://www.cdc.gov/drugoverdose/index.html>: “Drug overdose deaths continue to increase in the United States. From 1999 to 2017, more than 702,000 people have died from a drug overdose. In 2017, more than 70,000 people died from drug overdoses, making it a leading cause of injury-related death in the United States. Of those deaths, almost 68% involved a prescription or illicit opioid.” (emphasis added).

<sup>1557</sup> Anora M. Gaudiano, *How the Opioid Epidemic Is Exacerbating a US Labor-Market Shortage*, MarketWatch (June 29, 2018), <https://www.marketwatch.com/story/how-the-opioid-epidemic-is-exacerbating-a-us-labor-market-shortage-2018-06-28>.

<sup>1558</sup> Dale AM, *et al.* Predictors of long-term opioid use and opioid use disorder among construction works: Analysis of claims data. *Am J Ind Med*. 2021;64(1):48-57, at p. 48

force loss due to opioids estimates 919,400 individuals out of work  
force due to opioids in 2015.<sup>1559</sup>

c. Overdose (“OD”) deaths

- i. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: “Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. ... Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients.”<sup>1560</sup> The HRs from the Dunn study are represented in the graph at paragraph §C.12.c., below.
- ii. Dunn reported that 4 of the 51 overdose cases (7.8%) “had notes indicating overdoses associated with applying extra fentanyl patches or sucking on a patch.”<sup>1561</sup> The percentage of overdose cases attributed to fentanyl is much higher than the relatively minor percentage of patients in the study population who used the fentanyl patch (0.6%).<sup>1562</sup> This is consistent with fentanyl’s known lethality (50-100 times as potent as heroin), which increases the risk of overdose and death.
- iii. In the Dunn study, the authors noted that the risk analysis was based on a comparison of overdose events among higher dose patients to those who received lower doses, rather than the patients who received none.<sup>1563</sup> The authors also provided data on the rate of ODs at all levels of exposure, including those with no exposure, and these data further demonstrate the magnitude of increased risk. For the population with no prescribed opioids, the OD rate was 36 per 100,000 person years (PYR), while increasing to 677 per 100,000 PYR at doses of 50-99 mg, and 1791 per 100,000 PYR at doses of 100 mg or greater, representing rate increases of 18.8 and 49.8, respectively, compared to no prescription opioid use.<sup>1564</sup> These data are represented in the graph below:

<sup>1559</sup> Ben Gitis, Isabel Soto, *The Labor Force and Output Consequences of the Opioid Crisis*, American Action Forum (Mar. 27, 2018), <https://www.americanactionforum.org/research/labor-force-output-consequences-opioid-crisis/>.

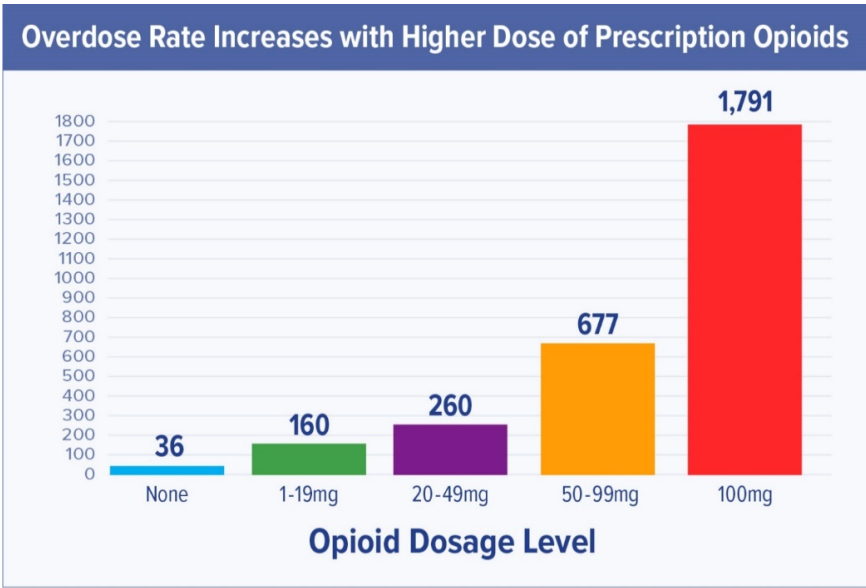
<sup>1560</sup> Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010;152(2):85-92, at p. 85.

<sup>1561</sup> *Id.* at p. 88.

<sup>1562</sup> *Id.* at Table 1, p. 88.

<sup>1563</sup> *Id.* at p. 90

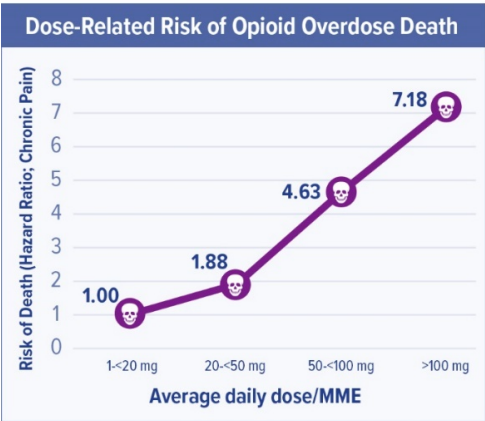
<sup>1564</sup> *Id.* at Table 3, p. 89.



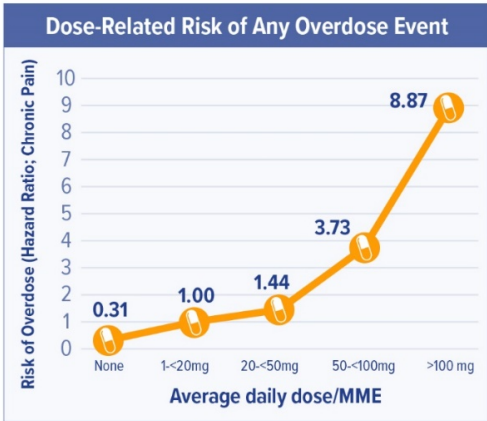
SOURCE: Dunn 2010

- iv. Dunn also noted that their study “provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses.”<sup>1565</sup> These are important data, since they directly refute the Industry’s position that only those who misuse the drugs are at risk of OUD and mortality.

**CDC: “HIGHER DOSAGE, HIGHER RISKS”**



SOURCE: Bohnert 2011



SOURCE: Dunn 2010

- v. As shown in the graph above, studies by Dunn *et al.* and by Bohnert *et al.* both found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MME. In the Dunn study, compared to the reference dose of 1-<20 mg,

<sup>1565</sup> *Id.* at p. 90.

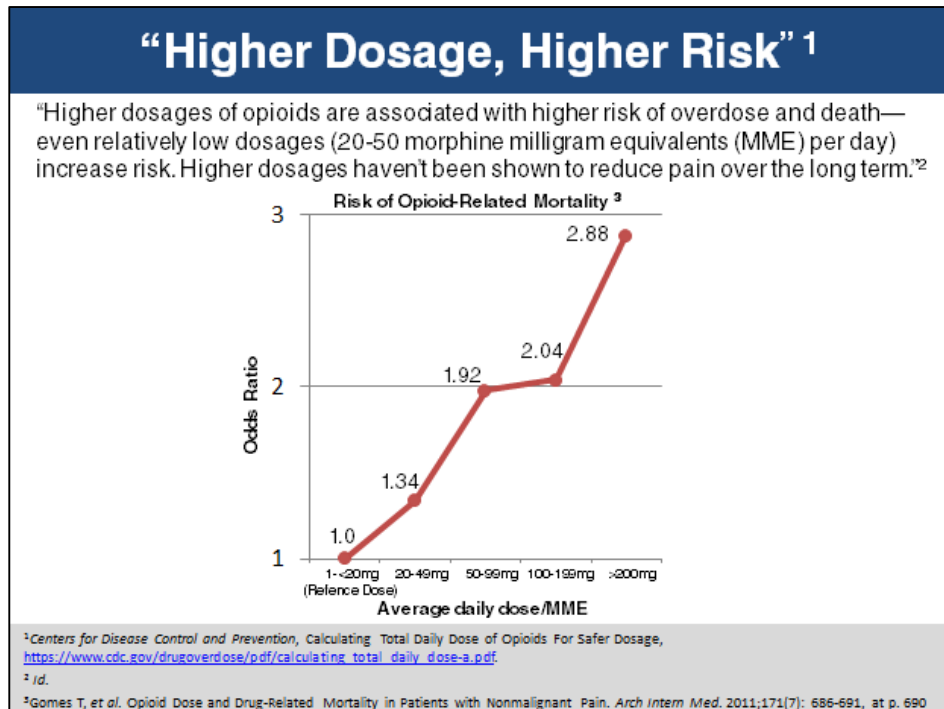
the adjusted hazard Ratio (HR) for 20-<50 mg was 1.44; for 50-100 mg, the HR was 3.73; and for > 100 mg, the HR was 8.87. In the Bohnert study, compared to the same reference dose of 1 to < 20 MME, the HR for 20 to < 50 mg was 1.88; for 50 to < 100 mg, the hazard ratio was 4.63; and at > 100 mg, the hazard ratio was 7.18. All results were statistically significant. A similar pattern held for each of three diagnostic groups in the Bohnert study (substance use disorders, chronic pain, and cancer): “The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR = 6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%).”<sup>1566</sup> Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

- vi. According to the CDC, the studies referenced above support the conclusion that approximately 60% of fatal prescription opioid overdoses occurred among patients taking medically prescribed opioids from a single prescriber.<sup>1567</sup>
- vii. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.<sup>1568</sup> This is illustrated in the graph below:

<sup>1566</sup> Bohnert, *et al.*, “Association Between Prescribing Patterns,” fn. 1467, above, at p. 1315; Olsen, *et al.*, “Pain relief that matters,” fn. 1179, above.

<sup>1567</sup> Paulozzi L, *et al.* CDC Grand Rounds: Prescription drug overdoses – a U.S. epidemic. *MMWR Morb Mortal Wkly Rep.* 2012;61(1):1-37, at p. 10. *See also:* Manchikanti, “ASIPP Guidelines,” fn. 415, above, at p. S10.

<sup>1568</sup> Gomes *et.al.*, “Opioid Dose,” fn. 1515, above, at p. 686. It is noteworthy that Gomes studied “Non-Malignant Pain,” without regard to duration of exposure, requiring only “at least one” opioid prescription in the 120 days prior to death. (p. 687) This may explain the lower relative risk in the Gomes study compared to those in Bohnert (study of pain patients specified those with “chronic pain” conditions) and Dunn (inclusion criteria required 3 or more opioid prescriptions within 90 days prior to the overdose). As Edlund demonstrated, duration of exposure is a key factor in determining the magnitude of increased risk of opioid-related harm.



- viii. A study of U.S. adolescents and young adults found that “approximately 1 in 10,000 adolescents and young adults overdosed while they had an active opioid prescription.”<sup>1569</sup> Further, in adjusted analyses “each increase in daily opioid dosage category was associated with an 18% higher odds of overdose.”<sup>1570</sup>
- ix. A recent retrospective cohort study of over 2 million individuals newly dispensed an opioid for pain between July 2013 and March 2016 found that 525 of 1121 overdoses (46.8%) occurred while patients were actively being treated with prescription opioids,<sup>1571</sup> which further supports that patients using opioids for medical reasons are at risk of overdose. The study further found that 289 of 1121 (25.5%) of the overdoses occurred within the first 28 days following initiation of the prescription and that the odds of long-term use (> 1 year) were 8-fold higher with > 30 days initial prescription compared to 2 days or less initial prescription length, and even prescriptions of 3-4 days conferred a 19% increased risk of OD compared to 2 days or less.<sup>1572</sup> While the study cannot rule out that patients may have been using non-prescribed opioids along with the prescribed opioids, the fact that nearly half were in active treatment, and that the risk increased with the prescribed dose,

<sup>1569</sup> Chua K-P, Brummett CM, Conti RM, Bohnert A. Association of opioid prescribing patterns with prescription opioid overdose in adolescents and young adults. *JAMA Pediatr.* 2020;174(2):141-148, at p. 146.

<sup>1570</sup> *Id.*

<sup>1571</sup> Gomes T, et al. Initial opioid prescription patterns and the risk of ongoing use and adverse outcomes. *Pharmacoepidemiol Drug Saf.* 2020:1-11, at p. 6.

<sup>1572</sup> *Id.* at pp. 6, 8.



strongly implicate the prescription opioids as at least contributing factors to the overdoses.

- x. A 2019 cohort study from the United Kingdom examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years. The authors found that “[l]ong-term opioid use is associated with serious adverse events such as major trauma, addiction and overdose. The risk increases with higher opioid doses.”<sup>1573</sup>
- xi. The evidence of increased dose as the cause of higher mortality is supported by evidence of the converse, that is, lower mortality following decreased dose. Recent experience in Oregon demonstrated a significant decrease in overdose deaths after policies were implemented to prioritize non-opioid pain management and to lower the doses when opioid therapy was prescribed.<sup>1574</sup>
- xii. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). The prescription opioid epidemic led to transition to heroin/fentanyl, and the cumulative death toll remains higher for prescription opioids, despite recent spikes in fentanyl-related mortality. Further, some researchers have noted a recent increase in stimulant involvement in opioid-related mortality, which varies by region, and is sometimes described as a “4<sup>th</sup> wave” of the opioid epidemic.<sup>1575</sup>
- xiii. Based on CDC data, between 1999 and 2018, 245,218 people died from opioid pain relievers (excluding non-methadone synthetics, predominantly fentanyl). In the same time period, 115,568 died from heroin, and 124,486 people died from non-methadone synthetics (predominantly fentanyl), for a total of 240,054 deaths due to heroin and illicit fentanyl. Although these numbers are staggering, the cumulative death toll from opioid pain relievers through 2018 (245,218) was more than that of heroin and illicit fentanyl combined

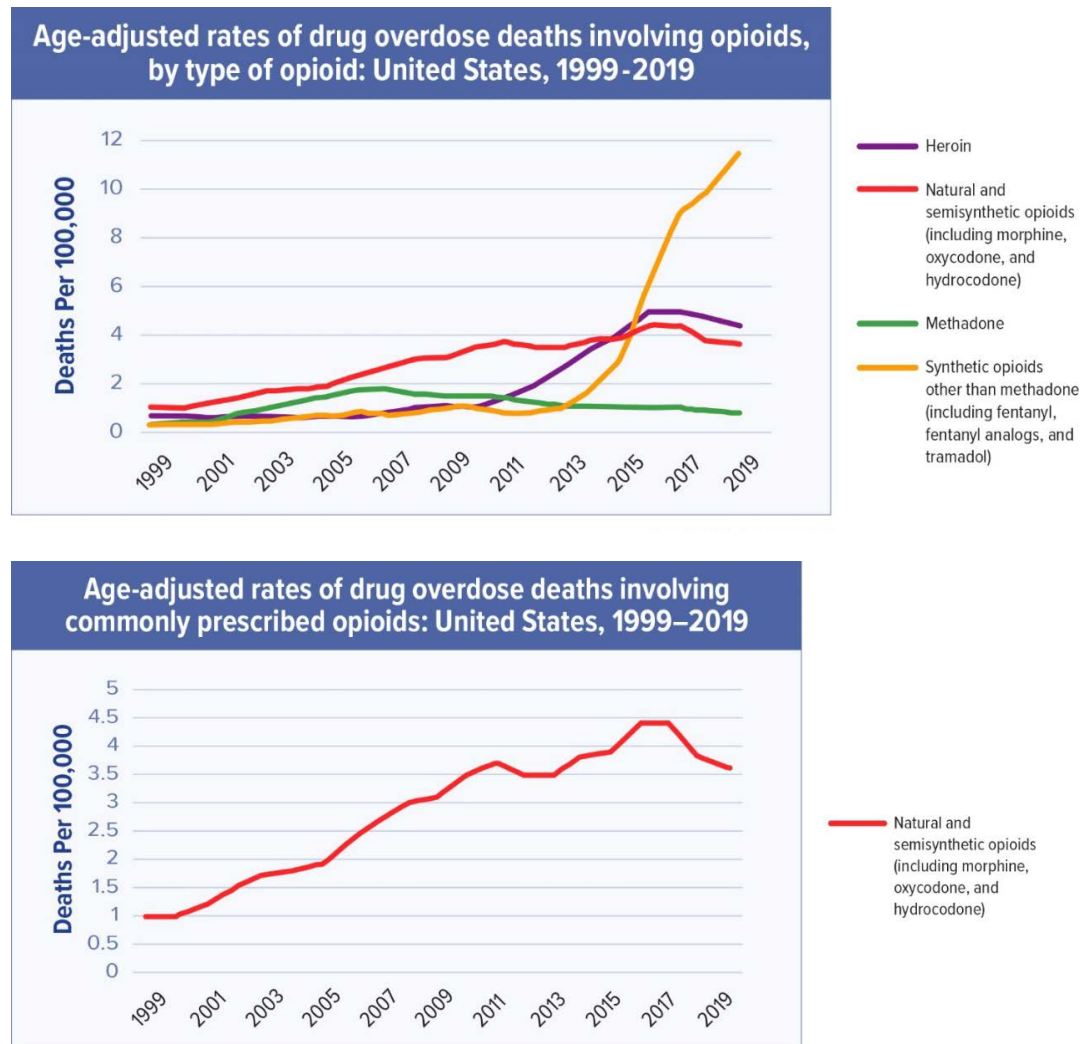
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<sup>1573</sup> Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: A cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019; 23:908-922, at p. 908.

<sup>1574</sup> Hedberg K, *et al.* Integrating public health and health care strategies to address the opioid epidemic: the Oregon Health Authority’s opioid initiative. *Journal of Public Health Management & Practice*. 2019;25(2):214-220, at pp. 214-215.

<sup>1575</sup> Friedman J, Shover CL. Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010-2021. *Addiction*. 2023;118:2477-2485. *See also:* O’Donnell J, *et al.* Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls – United States, 2019-2020. *MMWR*. 2021;70(50):1740-1746

(240,054).<sup>1576</sup> The graphs below show the changes in opioid death rates over time.<sup>1577</sup>



- xiv. Prescription opioid related deaths, excluding fentanyl and methadone, continued to rise through 2017, with 2018 registering the first substantial annual decline in prescription opioid related deaths since 1999 (14,495 deaths in 2017; 12,550 in 2018).<sup>1578</sup> A 2019 report released by the CDC shows that drug overdose deaths in women aged 30-64 years due to prescription opioids have been steadily rising

<sup>1576</sup> Centers for Disease Control and Prevention, *Data Brief 356. Drug Overdose Deaths in the United States, 1999–2018*, [https://www.cdc.gov/nchs/data/databriefs/db356\\_tables-508.pdf](https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf), at Data Table for Figure 3,

<sup>1577</sup> Graphs generated from data provided by *Id.*

<sup>1578</sup> *Id.*

between 1999 and 2017. “The crude rate for deaths involving prescription opioids increased from 1999 to 2017 for every age group, with the largest increases (>1,000%) among women aged 55–64 years.”<sup>1579</sup>

- xv. In 2019, 36,659 drug overdose deaths involved non-methadone synthetic opioids (primarily illicitly manufactured fentanyl), 14,019 deaths involved heroin and 14,626 deaths involved opioid pain relievers.<sup>1580</sup>
- xvi. Provisional data for the period May 2019-May 2020 show “the highest number of overdose deaths ever recorded in a 12-month period” with over 81,000 drug overdose deaths.<sup>1581</sup> Synthetic opioids (illicitly manufactured fentanyl) “appear to be the primary driver of the increases in overdose deaths” with 10 western states reporting an over 98% increase in fentanyl-involved overdose deaths.<sup>1582</sup> According to the CDC, “While overdose deaths were already increasing in the months preceding the 2019 novel coronavirus disease (COVID-19) pandemic, the latest numbers suggest an acceleration of overdose deaths during the pandemic.”<sup>1583</sup>
- xvii. Younger cohorts were particularly vulnerable to opioid-related mortality during the COVID-19 pandemic. In the years 2020 and 2021, more than 20% of deaths among those aged 20-39 years old and 10% of those aged 15-19 resulted from prescribed and/or unregulated opioids.<sup>1584</sup> “The absolute number of unintentional deaths due to opioid toxicity and the associated YLL [years of life lost] among those under 40 years far exceeded those attributable to COVID-19 in both 2020 and 2021.”<sup>1585</sup>
- xviii. Although the National Institute on Drug Abuse recently stated that “commonly prescribed opioids are no longer driving the overdose crisis”<sup>1586</sup> prescription opioids nevertheless remain a substantial

<sup>1579</sup> VanHouten JP, Rudd RA, Ballesteros MF, Mack KA. Drug Overdose Deaths Among Women Aged 30–64 Years — United States, 1999–2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(1):1-5, at p. 2.

<sup>1580</sup> Hedegaard H. *et al.* Drug overdose deaths in the United States, 1999-2019. NCHS Data Brief No. 394, at Data Table for Figure 3. <https://www.cdc.gov/nchs/products/databriefs/db394.htm>

<sup>1581</sup> Centers for Disease Control and Prevention, Overdose deaths accelerating during Covid-19, (December 17, 2020), <https://www.cdc.gov/media/releases/2020/p1218-overdose-deaths-covid-19.html>, at p. 1.

<sup>1582</sup> *Id.*

<sup>1583</sup> *Id.*

<sup>1584</sup> Gomes T, *et al.* Trends in opioid toxicity-related deaths in the US before and after the start of the COVID-19 pandemic, 2011-2021. *JAMA Network Open.* 2023;6(7):1-7, at p. 3.

<sup>1585</sup> *Id.*, at p. 5.

<sup>1586</sup> National Institute on Drug Abuse. *Drug Overdose Death Rates* (June 30, 2023), <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>

primary and contributing factor in US overdose mortality, as reflected in the chart below, based on government data:<sup>1587</sup>

Overdose deaths	2020	2021
Prescription Opioids (all)	16,416	16,706
Prescription Opioids and synthetic opioids other than Methadone	8,626	9,644
Prescription Opioids without synthetic opioids other than Methadone	7,790	7,062
Synthetic Opioids (primarily fentanyl)	56,516	70,601
Heroin (all)	13,165	9,173

xix. In short, as shown in the graphs above, while there has been an obvious recent spike in deaths related to heroin and illicit fentanyl, the number of deaths caused by non-fentanyl prescription opioids has continued to be unacceptably high, and approximately four times greater than in 1999.

d. Nonfatal overdose

- i. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, both in terms of medical costs to treat the overdose episode itself, and to provide long-term care for an OUD that may have given rise to the overdose event.
- ii. According to the CDC, among approximately 45 million emergency department visits reported by the 16 Enhanced State Opioid Overdose Surveillance (ESOOS) states from July 2016 through September 2017, “a total of 119,198 (26.7 per 10,000 visits) were suspected opioid overdoses.”<sup>1588</sup>
- iii. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into

<sup>1587</sup> National Institute on Drug Abuse. *National Drug Overdose (OD) Deaths*, 1999-2021 (excel file).

<sup>1588</sup> Vivolo-Kantor AM, Seth P, Gladden RM, *et al.* Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67:279–285, at p. 281.

categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.

- iv. A 2023 study of opioid overdose mortality risk following a non-fatal overdose found that in the year following the index overdose, the overdose incidence rate (fatal or non-fatal) was 23.3 per 100 person-years and that repeat opioid overdose incidence was highest in the first 30 days following the index overdose.<sup>1589</sup> Another 2023 study of opioid overdose found that 12.1% of opioid overdose survivors had a repeat overdose within 1 year.<sup>1590</sup> Despite evidence that medications for opioid use disorder (eg, buprenorphine, methadone) significantly reduce the risk of repeat opioid overdose,<sup>1591</sup> only 10.7% of patients received MOUD in the year after the index overdose.<sup>1592</sup>
- v. Tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In the paper by Dunn *et al.*, previously discussed, the authors found “[m]ore than 7 nonfatal overdose events occurred for each fatal overdose” in the study cohort.<sup>1593</sup> “The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious.”<sup>1594</sup> These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017<sup>1595</sup> would translate to over 100,000 nonfatal overdoses during that same year.

e. Suicide

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<sup>1589</sup> Hood JE, *et al.* Overdose and mortality risk following a non-fatal opioid overdose treated by Emergency Medical Services in King County, Washington. *Drug Alcohol Depend.* 2023;253:1-8, at p. 1.

<sup>1590</sup> Tipping AD, *et al.* Medications for opioid use disorder are associated with reduced risk of repeat overdose in Medicaid: A cohort study. *Journal of Substance Use and Addiction Treatment.* 2023. [journal pre-proof]

<sup>1591</sup> Heimer R, *et al.* Receipt of opioid use disorder treatment prior to fatal overdoses and comparison to no treatment in Connecticut, 2016-2017. *Drug and Alcohol Dependence.* 2023;254:1-7, at p. 1; *see also* Tipping, “Medications for opioid use disorder”, fn. 1590, above.

<sup>1592</sup> Tipping, “Medications for opioid use disorder”, fn. 1590, above.

<sup>1593</sup> Dunn, *et al.*, “Opioid Prescriptions,” fn. 1560, above, at p. 89.

<sup>1594</sup> *Id.*, p. 91.

<sup>1595</sup> CDC, Data Brief 356, fn. 1576, above, at p. 4.

- i. The 2019 cohort study from the United Kingdom which examined 98,140 new long-term (three or more opioid prescriptions within 90 days) opioid users for 3.4 years, and found that long-term use was associated with serious adverse events, also found that the risk of suicide by intentional overdose increases with higher opioid doses.”<sup>1596</sup> The authors also report that intentional opioid overdose was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).<sup>1597</sup>
- ii. Writing in the journal *Pain*, Ilgen *et al.* found that the higher the dose of opioids, the greater the suicide risk, an association which was not present in patients with chronic pain on acetaminophen, a non-opioid pain pill. The authors write, “Increased dose of opioids was found to be a marker of increased suicide risk, even when relevant demographic and clinical factors were statistically controlled . . . . There was no significant association between acetaminophen dose and regimen and suicide risk, suggesting that the observed effects may be specific to opioids.”<sup>1598</sup>
- iii. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that “A reduction in the quantity of prescribed opioids may function as a ‘means restriction’ by reducing patients’ access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients’ access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity. However, whether tapering changes the risk of either suicide or overdose is unknown.”<sup>1599</sup>
- iv. As above, intentional opioid overdose, *i.e.* suicide, was nearly 4x more likely in patients prescribed long-term opioids at the highest doses (>50mg).<sup>1600</sup>
- v. A Veterans Health Administration study examining the likelihood of death from overdose or suicide in veterans prescribed opioid analgesics in the early implementation period of VHA’s opioid safety initiative (2014-2016) found that “All patients exposed to opioids had an

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<sup>1596</sup> Bedson, “Risk of adverse events”, fn. 1573, above, at p. 908.

<sup>1597</sup> *Id.* at p. 913.

<sup>1598</sup> Ilgen MA, Bohnert AS, *et al.* Opioid Dose and Risk of Suicide. *Pain*. 2016 May; 157(5): 1079–1084. doi:10.1097/j.pain.0000000000000484, at p. 5.

<sup>1599</sup> Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76.

<sup>1600</sup> Bedson *et al.* “Risk of Adverse Events”, fn. 1573, above, at p. 913.



increased risk of death from overdose or suicide after starting or stopping treatment with opioids. Although patients treated with opioids for long periods (e.g., >400 days in our evaluation) had the highest hazard ratios after stopping treatment, even those treated for up to 30 days had a rise in the risk of death after treatment was stopped (hazard ratio of 1.4 for death from overdose after stopping opioid treatment and 1.7 for death from overdose or suicide). Those treated with opioids for 31-90 days had a hazard ratio of 2.4 for death from overdose after stopping opioid treatment (2.8 for death from overdose or suicide).<sup>1601</sup> In other words, opioids increase the risk of overdose death in the initiation phase, the maintenance phase, and the discontinuation phase, highlighting the lethality of these drugs at all stages of treatment. Further, risks increase with increasing dose and duration.<sup>1602</sup>

- f. Opioids are associated with more adverse medical outcomes and increased mortality and morbidity than non-opioid analgesics (NSAIDs),<sup>1603</sup> contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDs) for pain are comparable.<sup>1604</sup>
- g. The opioid epidemic is also partly responsible for the spread of Hepatitis C, HIV and other infectious diseases across the country in recent years, as people who become addicted to prescription opioids, transition to injection drug use and share needles with others who are infected. For example, the outbreak of Hepatitis C and HIV in Scott County, Indiana in 2015, “resulted from inappropriate prescribing of opioid medications.”<sup>1605</sup>
- h. Misuse and addiction
  - i. As discussed in this report, above, misuse of prescription opioids and addiction are significant problems throughout the United States; prescription opioids have been a major stepping stone for illicit opioid use and resulting harms; and over-prescribing contributes to population risk of opioid related harms.

<sup>1601</sup> Oliva EM, *et al.* Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: Observational evaluation. *BMJ*. 2020;368:m283:1-10, at p. 6. The study “did not take into consideration the reasons or clinical intentions for stopping, or the speed of its execution.”

<sup>1602</sup> *Id.* at p. 6.

<sup>1603</sup> Solomon DH, Rassen Ja, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

<sup>1604</sup> Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, non-opioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

<sup>1605</sup> Strathdee SA, Beyrer C. Threading the Needle — How to Stop the HIV Outbreak in Rural Indiana. *N Engl J Med*. 2015. doi:10.1056/NEJMp1507252, at p. 398.

- ii. 11 million people misused prescription opioids in 2016, compared to the approximately 1 million people using heroin. In 2011, according to a CDC report, 11 million people reported nonmedical use of opioid analgesics. “Moreover, chronic nonmedical use of opioid analgesics (*i.e.* nonmedical use on 200 days or more in the past year) increased roughly 75% between 2002-2003 and 2009-2010. This increase means that on average in 2009-2010 there were nearly 1 million people in the U.S. with chronic nonmedical use of opioid analgesics.”<sup>1606</sup>
- iii. Nearly 2 million (0.8%) of people in the United States are addicted to opioids based on estimates from the 2015 National Survey on Drug Use and Health (NSDUH).<sup>1607</sup>
- iv. Even among cancer patients, the rates of opioid misuse and addiction is very high, with a recent study finding that 19% of cancer patients taking opioids for cancer pain develop nonmedical opioid use (*i.e.*, misuse) within a median duration of 8 weeks after initial supportive care clinic consultation.<sup>1608</sup>
- v. The opioid epidemic may be contributing to the risk of dementia. Evidence has shown that the longer term consequences of opioid use disorder include an 88% higher risk for developing Alzheimer’s Disease/dementia within 1 year compared to those without OUD (aHR=1.88, 95% CI 1.74, 2.03) and a 211% higher risk for developing Alzheimer’s Disease/dementia (aHR=3.11, 95% CI 2.63, 3.69) within 10 years.<sup>1609</sup>

**13. There is no doubt that a cause-and-effect relationship exists between the oversupply of prescription opioids and the opioid epidemic.**

- i. Defense experts in this litigation have repeatedly and mistakenly claimed that the prescription opioid oversupply and the opioid epidemic

<sup>1606</sup> United States Dep’t of Health and Human Servs. *Addressing Prescription Drug Abuse in the United States*. 1-36, at pp., 9-10, [https://www.cdc.gov/drugoverdose/pdf/hhs\\_prescription\\_drug\\_abuse\\_report\\_09.2013.pdf](https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf).

<sup>1607</sup> Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Annals of Internal Medicine*. 2017;167(5):293-301. Epub 2017/08/02. doi: 10.7326/m17-0865. PubMed PMID: 28761945, at 293.

<sup>1608</sup> Yennurajalingam S, *et al.* Frequency of and factors associated with nonmedical opioid use behavior among patients with cancer receiving opioids for cancer pain. *JAMA Oncol*. 2021;1-8. Doi:10.1001/jamaoncol.2020.6789, at 1.

<sup>1609</sup> Qeadan F, *et al.* Exploring the association between opioid use disorder and Alzheimer’s disease and dementia among a national sample of the US population. *Journal of Alzheimer’s Disease*. 2023;96(1):229-244, at p. 229 and Table 2. While the authors acknowledge that the exact underlying mechanisms between OUD and the onset of dementia remain to be fully elucidated, chronic opioid use and abuse has been associated with brain inflammation and prolonged periods of hypoxia which are in turn associated with the onset of dementia.

are associated but not causally linked.<sup>1610</sup> Defendants’ denial of causation parallels the history of smoking and cancer. For much of the 20<sup>th</sup> century, scientific literature had reported an “association” between exposure to cigarettes and the occurrence of lung cancer, that is, lung cancer was found to have occurred more frequently among smokers. However, cigarette manufacturers denied that their products had “caused” the increased number of lung cancer cases and relied upon publications that attributed the association to other factors.

- ii. In 1956, the noted British epidemiologists, Sir Richard Doll and Sir Austin Bradford Hill published an influential study of smoking and lung cancer among physicians in Britain. This article recounted and rejected alternative explanations for the increase in lung cancer, *e.g.*, “that smoking does not produce cancer in a person in whom cancer would not otherwise have occurred at all, but merely determines the primary site of a growth that is destined to appear in some part of the body,”<sup>1611</sup> and that “atmospheric pollution” might explain the increased risk.<sup>1612</sup>
- iii. Doll and Hill observed a higher mortality in smokers than in non-smokers, a higher mortality in heavy smokers than in light smokers, and a higher mortality in those who continued to smoke than in those who gave it up.<sup>1613</sup> In 1964, their study became part of the data set that resulted in the 1964 Report of the United States Surgeon General that “cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs other

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<sup>1610</sup> See, *e.g.*, Expert Report of Rob Lyerla. *In re: Nat’l Prescription Opiate Litig.*, No. 1:17-MD-2804 (May 10, 2019) (“Plaintiffs’ experts purport to demonstrate a causal relationship between opioid use and opioid misuse and mortality. However, the data they use are insufficient to support their conclusions.”), Expert Report of Stephanie W. Colston, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“A substantial body of empirical evidence documents that prescription opioids are not the causal culprit of the opioids abuse crisis. These studies document that the root causes of the opioid abuse crisis are considerably broader than supply alone and, in addition, the studies demonstrate that supply-only responses to the opioids abuse crisis have had deleterious public health and safety consequences.”), Expert Report of Peggy Compton, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“persons with opioid use disorder will seek opioids from many sources, including a physician, however this should not be interpreted to mean that the prescribed opioid is causally related to the development of addiction.”), and Expert Report of Kevin M. Murphy, *City of Huntington, West Virginia et al. v. AmerisourceBergen Drug Corporation et al.*, Case No. 3:17-01362 (August 27, 2020) (“An association between opioid supply and opioid mortality (or other opioid-related harms) does not establish a causal link.”).

<sup>1611</sup> Doll and Hill. Lung Cancer and Other Causes of Death in Relation to Smoking: A Second Report on the Mortality of British Doctors. *British Medical Journal*, 1956, 1071-1081, at 1077.

<sup>1612</sup> *Id.* at 1078.

<sup>1613</sup> *Id.* at 1081.

factors. The data for women, though less extensive, point in the same direction.”<sup>1614</sup>

- iv. In 1965, one of the authors of that landmark smoking study, Sir Austin Bradford Hill, published an essay that has become the framework for answering the question of when a statistical finding of association meets threshold criteria for causation: “What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”<sup>1615</sup> The “Bradford Hill factors,” as they have become known, are generally accepted in the scientific literature, as the leading methodology to determine whether there is a causal relationship between exposure to a risk factor and the occurrence of disease.<sup>1616</sup>
- v. The factors cited by Bradford Hill to determine whether an association is causal are as follows: (1) Strength of the association, (2) Consistency, (3) Specificity (4) Temporality, (5) Dose-response relationship, sometimes called “biological gradient,” (6) Plausibility (7) Coherence, (8) Experiment,<sup>1617</sup> and (9) Analogy. These factors are a guide, not a checklist: “There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One or more factors may be absent even when a true causal relationship exists. Similarly, the existence of some factors does not ensure that a causal relationship exists. Drawing causal inferences after finding an association and considering these factors requires judgment and searching analysis, based on biology, of why a factor or factors may be absent despite a causal relationship, and vice versa. Although the

<sup>1614</sup> Report of the Advisory Committee to the Surgeon General, *Smoking and Health*. Public Health Service Publication No.1103, January 1964. <https://profiles.nlm.nih.gov/spotlight/nn/catalog.nlm:nlmuid-101584932X204-doc>, at 31.

<sup>1615</sup> Hill AB, *The Environment and Disease*, fn. 105, above.

<sup>1616</sup> I am aware that Judge Polster cited the Bradford-Hill factors, and the Federal Judicial Center’s *Reference Manual on Scientific Evidence* that lists those factors, in his Order denying the MDL Defendants’ motion to exclude my opinions. See Order Denying Defendants’ Motion to Exclude Expert Testimony of Katherine Keyes, Anna Lembke and Jonathan Gruber re the “Gateway Hypothesis” of Causation, *In re: Nat’l Prescription Opiate Litig.*, No. 1:17-MD-2804, 2019 WL 4043943 (N.D. Ohio Aug. 26, 2019), at 11-12.

<sup>1617</sup> The factor of “Experiment” is referred to as “Cessation of Exposure” in the set of “Hill factors” provided by the Federal Judicial Center, *Reference Manual on Scientific Evidence* (3rd edition, 2011), which states: “If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with *cigarette smoking and lung cancer*.... [W]hen such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.” (*Id.* at 605; emphasis added). This formulation closely matches Bradford Hill’s description of the “Experiment” factor: “Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association *some preventive action is taken. Does it in fact prevent?* The dust in the workshop is reduced, lubricating oils are changed, *persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed.*” Hill AB, *The Environment and Disease*, fn. 105, above, at 298-299 (emphasis added).

drawing of causal inferences is informed by scientific expertise, it is not a determination that is made by using an objective or algorithmic methodology. These guidelines reflect criteria proposed by the U.S. Surgeon General in 1964 in assessing the relationship between smoking and lung cancer and expanded upon by Sir Austin Bradford Hill in 1965 and are often referred to as the Hill criteria or Hill factors.”<sup>1618</sup>

- vi. As summarized below, the sources cited in this Report provide more than sufficient evidence that there is a causal relationship between prescription opioids, their oversupply, and the various harms described, based on this generally accepted methodology. There are numerous parallels to the relationship between smoking and lung cancer, including strength of association, dose-response relationship, temporality, and consistency across multiple studies. An additional parallel is that widespread increased access to and promotion of cigarettes gave rise to more young people starting smoking and fewer users quitting; as well as contributed to greater consumption among users across the United States.<sup>1619</sup>
- vii. In evaluating the evidence, the factors of strength of association, consistency, temporality, dose-response, biological plausibility, and experiment/cessation of exposure are most important.
- viii. Bradford Hill’s article states as follows: “(1) *Strength*. First upon my list I would put the strength of the association.”<sup>1620</sup> Regarding this factor, the *Reference Manual on Scientific Evidence* states: “The relative risk is one of the cornerstones for causal inferences. Relative risk measures the strength of the association. The higher the relative risk, the greater the likelihood that the relationship is causal. For cigarette smoking, for example, the estimated relative risk for lung cancer is very high, about 10. That is, the risk of lung cancer in smokers is approximately 10 times the risk in nonsmokers. A relative risk of 10, as seen with smoking and lung cancer, is so high that it is extremely difficult to imagine any bias or confounding factor that might account for it. The higher the relative risk, the stronger the association and the lower the chance that the effect is spurious.”<sup>1621</sup>
- ix. A standard textbook in epidemiology, written by a Professor at the Harvard School of Public Health, describes ratios of between 3.0 and

<sup>1618</sup> Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 599-600.

<sup>1619</sup> U.S. Surgeon General, *Preventing Tobacco Use Among Youth and Young Adults*, 2012, at Chapter 5, p. 487.

<sup>1620</sup> Hill AB, *The Environment and Disease*, fn. 105, above, at 295. (emphasis in original).

<sup>1621</sup> Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 602. *See also*, 1964 Surgeon General’s report at Table 2, p. 29, citing 10.8x higher rate of lung cancer among smokers compared to non-smokers.

10.0 as “strong,” and a ratio of over 10.0 as “infinite,” meaning that it is extremely unlikely to be explained by any confounding or bias.<sup>1622</sup>

- x. There are two complementary and mutually reinforcing perspectives to view the strength of association between prescription opioids and adverse outcomes such as addiction and mortality. First is the association found in specific exposed populations; second is the association found on a national level, as a result of prescription opioid promotion, sale, and distribution. These are addressed below.
- xi. Strength of association in specific exposed populations: The evidence in this case shows “strong” and even “infinite” ratios of death and disease among specific populations exposed to prescription opioids, compared to unexposed subjects. The peer-reviewed Edlund study discussed at Section §C.4.f., analyzed claims and prescription information from two large healthcare databases. The study reported exceptionally high hazard ratios (HRs) of 14.92, 28.69, and 122.45 for diagnosis of opioid addiction among subjects with low, moderate, and high-dose chronic (> 90 days) exposure to prescription opioids, respectively, compared to subjects with no exposure to prescription opioids. All of these ratios exceed the relative risk of 10 for smoking and lung cancer, and also exceed a threshold for “infinite” association. Indeed, for patients on prescription opioids equivalent to 120 mg of morphine daily for three months or more, the risk of becoming addicted to opioids as a result of that prescription is more than ten times the risk of developing lung cancer as a result of smoking cigarettes. The data therefore provide exceptionally strong support for causality of opioid addiction by chronic exposure to prescription opioids.
- xii. Strong associations are also demonstrated between prescription opioid exposure and fatal/nonfatal overdose, among specific populations. The peer-reviewed study by Dunn, discussed in Section §C.12.c. of this Report, reported HR of 8.87 for opioid overdose, including fatal and non-fatal, among members of a Washington State healthcare organization who were exposed to prescription opioids > 100 MME per day, compared to subjects without prescription opioid exposure; the Bohnert study, also discussed at Section §C.12.c., showed a similar HR of 7.19 for fatal overdose among Veterans Health Administration patients exposed to > 100 MME per day, compared to subjects with < 20 MME per day. Both of these HRs are toward the upper end of the “strong” category of association. Defense experts fail to address the importance of these strong associations that support causation.
- xiii. Analogous increased rates of prescription opioid overdose have been demonstrated in state and national data sets since the oversupply began

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<sup>1622</sup> See, e.g., Monson, Richard. *Occupational Epidemiology*. CRC Press. (2nd edition, 1990), at 88.



in the late 1990s. “From 1999 to 2007 in Ohio, there were increases of 304 percent and 325 percent, respectively in the unintentional drug poisoning death rate and total grams of prescription opioids distributed per 100,000 population.”<sup>1623</sup> Based on these data, the Ohio Department of Health concluded, “There is a *strong relationship* between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”<sup>1624</sup> This “strong” relationship was enabled by widespread distribution, resulting in over a three-fold increase in per capita prescriptions. Similar increased prescription opioid sales, distribution, mortality and hospitalization occurred nationally, as shown in Section §C.3.b of this Report. As noted by CDC authors, “Increased use of OPR [Opioid pain Relievers] has contributed to the overall increases in rates of overdose death and nonmedical use, and variation among states in OPR sales probably contributes to state variation in these outcomes.”<sup>1625</sup>

- xiv. There is essentially uniform agreement in the published literature that promotion and widespread distribution of prescription opioids resulted in the oversupply that gave rise to the epidemic of addiction and mortality. As noted previously, the NASEM and ASPPH reports, both highly reputable and respected sources, identified aggressive marketing, including misleading promotion by some, as well as distribution throughout the country, as key factors contributing to the epidemic.<sup>1626</sup>
- xv. (2) *Consistency* refers to whether similar findings have been “repeatedly observed by different persons, in different places, circumstances and times.”<sup>1627</sup> As with the factor of “Strength of Association,” *Consistency* is also apparent in specific study populations as well as state and national data sets. Numerous references cited in this Report provide consistency of the observed relationship between

<sup>1623</sup> Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at 2. [https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic\\_of\\_Prescription\\_Drug\\_Overdose\\_Ohio\\_Report.pdf?MOD=AJPERES&CONVERT\\_TO=url&CACHEID=ROOTWORKSPACE.Z18\\_M1HGK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3](https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3)

<sup>1624</sup> *Id.*, (emphasis added).

<sup>1625</sup> Paulozzi, *et al.*, Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008. *MMWR*, November 4, 2011 / 60(43):1487-1492. *See also*, Walley, Alexander Y., *et al.* “The contribution of prescribed and illicit opioids to fatal overdoses in Massachusetts, 2013-2015.” *Public Health Reports* 134.6 (2019): 667-674., <https://doi.org/10.1177/0033354919878429>, at 667. “In the United States in the 1990s and early 2000s, annual increases in opioid-related overdose deaths and entries into treatment for opioid addiction paralleled increases in prescriptions of opioid medications for pain. *This correlation appears to have been causal*, as the expansion of opioid prescribing for pain led to more persons overdosing on opioids and more persons seeking treatment for opioid use disorder.” (emphasis added).

<sup>1626</sup> *See* Section §C.2.j. of this Report, above.

<sup>1627</sup> Hill AB, *The Environment and Disease*, fn. 105, above, at 296. (emphasis in original)

prescription opioids and the adverse outcomes of opioid addiction and overdose in particular populations.

- xvi. Consistent with the Edlund study, Papadomanolakis-Pakis was an incidence study that reported risk of opioid addiction among Ontario, Canada residents whose records were part of a healthcare database; HRs in that study increased with duration of the initial opioid prescription.<sup>1628</sup> As discussed in Section §C.8.b of this Report, the Vowles systematic review found elevated risks of addiction and misuse in 38 studies of chronic pain patients exposed to prescription opioids, and the Boscarino study reported similarly elevated risks.
- xvii. The relationship between increased prescription *opioid sales* and increased drug overdose mortality has also been demonstrated repeatedly, and consistently. As noted above in the discussion of Strength of Association, the Ohio Department of Health reported, based on data from 1999-2009, “There is a strong relationship between increases in sales of prescription opioids and fatal unintentional drug poisoning rates.”<sup>1629</sup> The CDC data showed a similar relationship at the national level.<sup>1630</sup> These similar findings support the Hill factor of Consistency, as well as Strength of Association.
- xviii. (3) *Temporality*: “A temporal, or chronological, relationship must exist for causation to exist. If an exposure causes disease, the exposure must occur before the disease develops. If the exposure occurs after the disease develops, it cannot have caused the disease.” *Temporality* is established in both specific study populations and national data sets.
- xix. The incidence studies (Edlund, Papadomanolakis-Pakis) cited above demonstrate that diagnoses of opioid addiction followed exposure to prescription opioids, since the study designs excluded subjects with opioid addiction prior to the beginning of the study period. Temporality was also shown in a study reporting that “exposure to opioids through a dental clinician in a population of opioid naïve patients was associated with higher use of opioids at 90 to 365 days later and subsequent diagnoses associated with opioid abuse or overdose compared with controls. ... [T]he higher probability of abuse diagnoses in the exposed

<sup>1628</sup> Papadomanolakis-Pakis, N, *et al.* Prescription opioid characteristics at initiation for non-cancer pain and risk of treated opioid use disorder: A population-based study. *Drug and Alcohol Dependence*. 2021:221:1-9.

<sup>1629</sup> Ohio Department of Health, Violence and Injury Prevention Program. “Epidemic of Prescription Drug Overdose in Ohio, 1999-2009,” July 18, 2018, at p.2. [https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic\\_of\\_Prescription\\_Drug\\_Overdose\\_Ohio\\_Report.pdf?MOD=AJPERES&CONVERT\\_TO=url&CACHEID=ROOTWORKSPACE.Z18\\_M1HGGIK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3](https://odh.ohio.gov/wps/wcm/connect/gov/5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c/Epidemic_of_Prescription_Drug_Overdose_Ohio_Report.pdf?MOD=AJPERES&CONVERT_TO=url&CACHEID=ROOTWORKSPACE.Z18_M1HGGIK0N0JO00QO9DDDDM3000-5a0bbf8a-8d88-49e5-bd6c-56ca28c2104c-miUpbk3)

<sup>1630</sup> See data and graph at Section §C.3.b above.

cohort suggests that many of the repeated opioid prescriptions in this cohort were related to substance abuse.”<sup>1631</sup> The authors reported subsequent opioid prescriptions at 90 to 365 days among 6.9% of the dental patients who received opioids, compared to only 0.1% of those treated with non-opioids.<sup>1632</sup>

- xx. In state and national data, a temporal relationship also has been documented between increased distribution of prescription opioids and increased mortality, in the CDC and state-specific data, as referenced above and in Appendix III.<sup>1633</sup>
- xxi. *Temporality* also exists with respect to the Gateway Effect, as documented by undisputed evidence that increased use and misuse of prescription opioids preceded the second and third waves of the epidemic involving the transition from prescription opioids to heroin and fentanyl. Muhuri and others documented the fact that 70-80% of recent heroin users had previously used prescription opioids.<sup>1634</sup> McCabe, Lankenau and Mars all demonstrated that this transition occurred after both medical use (pursuant to a doctor’s prescription) and nonmedical use (outside the parameters of a doctor’s prescription).<sup>1635</sup>
- xxii. (4) *Dose-response*: “[I]f the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers.”<sup>1636</sup>
- xxiii. Numerous studies cited above provide clear and convincing evidence of a dose-response relationship, including but not limited to Edlund,

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<sup>1631</sup> Schroeder, *et al.*, Association of Opioid Prescriptions from Dental Clinicians for US Adolescents and Young Adults with Subsequent Opioid Use and Abuse. *JAMA Internal Medicine* 2018; doi:10.1001/jamainternmed.2018.5419, at E5.

<sup>1632</sup> *Id.* at E3-E4.

<sup>1633</sup> Similarly, in the 1964 Surgeon General’s Advisory Committee Report on Smoking and Health, the increase in lung cancer was observed in the context of large increases in exposure to cigarettes: “Nearly 70 million people in the United States consume tobacco regularly. Cigarette consumption in the United States has increased markedly since the turn of the Century, when per capita consumption was less than 50 cigarettes per year,” and cigarette consumption rose from 138 per person in 1910 to a “peak of 3,986 [per person] in 1961.” 1964 Surgeon General’s Report, fn.1614, above, at 26. This stark increase in tobacco consumption has a parallel in the large-scale increased distribution of opioids between the 1990s and 2012, with only a modest decline since that time.

<sup>1634</sup> Report, above, at §C.9.h.

<sup>1635</sup> Report, above, at §C.9.h.

<sup>1636</sup> Hill AB, The Environment and Disease, fn. 105, above, at p. 298. (emphasis in original). *See also*, 1964 Surgeon General’s Report, fn. 1614, above, at p. 35: “The death rates increase with the amount smoked.”

Dunn, Bohnert, and Papadomanolakis-Pakis, all of which found increased risk of either opioid addiction or overdose with greater exposure to prescription opioids.

- xxiv. An analogous result is found with regard to the “Gateway Effect,” in that more frequent misuse of prescription opioids is associated with a higher rate of transition to heroin.<sup>1637</sup> A CDC publication similarly reported, “Drug abuse and overdose rates increased with longer use,”<sup>1638</sup> and another CDC publication simply stated: “Higher Dosage, Higher Risk,”<sup>1639</sup> neatly summarizing the evidence of a dose-response relationship between prescription opioids and overdose.
- xxv. Dose-response was also found in a study reporting that odds of overdose were significantly greater with increasing amounts of opioids dispensed to family members (>0-<50 morphine milligram equivalents per day: OR, 2.71 [95% CI, 2.42-3.03]; 50-<90 morphine milligram equivalents per day: OR, 7.80 [95% CI, 3.63-16.78]; ≥90 morphine milligram equivalents per day: OR, 15.08 [95% CI, 8.66-26.27]).<sup>1640</sup> These findings are of particular importance in demonstrating the causal relationship between oversupply and opioid overdose, since overprescribing provides a source for excess opioid pills that are diverted from the original recipient to family members who suffer the adverse effects.
- xxvi. *Dose-response* has similarly been shown with respect to promotion, sale and distribution of opioids. In the Hadland studies described previously, the authors explicitly stated that their data showed a dose-response relationship between opioid manufacturers’ marketing and the occurrence of opioid prescribing, with each additional industry-sponsored meal associated with additional opioid prescribing.<sup>1641</sup>
- xxvii. ARCOS data on opioid sales also strongly support Dose-response on a population scale. “Death rates from opioids soared in the towns, cities and counties that were saturated with billions of prescription pain pills from 2006 through 2012, according to government death data and a

<sup>1637</sup> Jones CM, Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010. *Drug Alcohol Depend.* 2013;132(1-2):95-100, at 95.

<sup>1638</sup> Paulozzi LJ, *et al.* Risk of Adverse Health Outcomes with Increasing Duration and Regularity of Opioid Therapy. *J Am Board Fam Med.* 2014 ; 27(3): 329–338, at p. 329. doi:10.3122/jabfm.2014.03.130290, at 329.

<sup>1639</sup> Centers for Disease Control and Prevention, Calculating Total Daily Dose of Opioids for Safer Dosage. [https://www.cdc.gov/drugoverdose/pdf/calculating\\_total\\_daily\\_dose-a.pdf](https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf), at 1.

<sup>1640</sup> Khan, *et al.*, Association of Opioid Overdose with Opioid Prescriptions to Family Members. *JAMA Internal Medicine* (2019), doi:10.1001/jamainternmed.2019.1064, at E-3.

<sup>1641</sup> Hadland SE, *et al.* In Reply. *JAMA.* 2018;178(10):1426-1427 at 1426.

previously undisclosed database of opioid shipments made public this week. ... The national death rate from opioids was 4.6 deaths per 100,000 residents. But the *counties that had the most pills distributed per person experienced more than three times that rate on average.*"<sup>1642</sup> My colleague at Stanford, Keith Humphreys, who served as a drug policy adviser to the George W. Bush and Obama administrations, "said the *correlation of opioid deaths and pain pill distribution could be expected.* 'These horrible death rates should not surprise anyone,' Humphreys said. 'The *supply of drugs matters enormously no matter what else we try to do. When there's a flood of addictive drugs, lots of people end up being harmed*'." <sup>1643</sup>

- xxviii. A further example of *dose-response* at the population level is found in a 2019 study by Ghertner, documenting the relationship between opioid sales (ARCOS data) with county-level opioid-related hospitalization rates. Ghertner reported that there was a 9% increase in opioid-related hospitalizations for each one morphine kilogram equivalent increase in opioid sales.<sup>1644</sup> This study further documents that the *Dose-response* factor is operative at both the personal and population levels, with respect to individual exposures as well as widespread promotion and distribution to the nation as a whole.
- xxix. (6) *Plausibility*: "Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops. When biological plausibility exists, it lends credence to an inference of causality."<sup>1645</sup>
- xxx. In this case, biological plausibility of prescription opioids as the cause of the various harms described in this Report has been established by the evidence detailed in Sections §C.1 and §C.2, above. In summary, the molecular similarity between prescription opioids and heroin, the impact of these molecules on the dopamine system and the development of the disease of addiction, and their effects on respiratory suppression (slowed breathing) and bradycardia (lowered heart rate) as the cause of overdose death, are well-documented and established. It is similarly well-known that the phenomenon of tolerance is common,

<sup>1642</sup> Horwitz, *et al.* Opioid death rates soared in communities where pain pills flowed. (July 17, 2019) [https://www.washingtonpost.com/investigations/opioid-death-rates-soared-in-communities-where-pain-pills-flowed/2019/07/17/f3595da4-a8a4-11e9-a3a6-ab670962db05\\_story.html](https://www.washingtonpost.com/investigations/opioid-death-rates-soared-in-communities-where-pain-pills-flowed/2019/07/17/f3595da4-a8a4-11e9-a3a6-ab670962db05_story.html), at 1 (emphasis added).

<sup>1643</sup> *Id.* at 4 (emphasis added). To the best of my knowledge, Professor Humphreys is not a retained witness in any opioid litigation.

<sup>1644</sup> Ghertner, R. U.S. county prevalence of retail prescription opioid sales and opioid-related hospitalizations from 2011 to 2014. *Drug Alcohol Depend.* 2019;194:330-335. doi:<https://doi.org/10.1016/j.drugalcdep.2018.10.031>, at 330.

<sup>1645</sup> Federal Judicial Center, *Reference Manual on Scientific Evidence*, 3rd edition, 2011, at 604.

requiring prescription opioid users to increase the dose to achieve the same effect, thereby increasing the risk in accordance with the dose-response effects documented above.

- xxxii. *Experiment:* As mentioned above, this factor refers to the effects of prevention or cessation of exposure in reducing disease. CDC data show that “Opioid prescribing has declined substantially across the United States between 2014 and 2017,”<sup>1646</sup> and that prescription opioid-involved overdose death rates decreased by 13.5% from 2017-2018.<sup>1647</sup> Also, a recent Continuing Medical Education publication stated, “Patients with opioid problems may have extended periods of abstinence and usually do well. However, there is a chronic risk of accidental overdose, trauma, suicide, and infectious diseases. *The risk decreases with abstinence from opioids.*”<sup>1648</sup>
- xxxiii. *Summary:* According to the generally accepted methods described above, it is clear that widespread sale and distribution of prescription opioids has resulted in exposures that are causally related to the epidemics of fatal and non-fatal opioid overdose, opioid addiction, and transition to illicit opioid use.

**14. For the reasons explained, the Pharmaceutical Opioid Industry bears responsibility for the misrepresentation of safety and efficacy, the ubiquitous distribution of prescription opioids, and the unchecked dispensing of prescription opioids, which resulted in the ongoing epidemic. To the extent that other factors contributed, those conditions were exploited by the Industry to increase the extent of harm.**

- a. As I wrote in my book, *Drug Dealer, MD*,<sup>1649</sup> doctors were “duped” by the myths that the risk of addiction to prescription opioids was “rare,” and that the drugs were beneficial for chronic pain. I also wrote at that time, and I continue to hold the opinion, that others had some responsibility for the opioid epidemic.
- b. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. It is responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, *Drug Dealer, MD*, I

<sup>1646</sup> Kuehn B. (2019). Declining Opioid Prescriptions. *JAMA*, 321(8), 736. <https://doi.org/10.1001/jama.2019.0647>

<sup>1647</sup> Centers for Disease Control and Prevention, Press Release, New Data Show Significant Changes in Drug Overdose Deaths (March 18, 2020) <https://www.cdc.gov/media/releases/2020/p0318-data-show-changes-overdose-deaths.html>

<sup>1648</sup> Dydyk, A. M., Jain, N. K., & Gupta, M. (2020). Opioid Use Disorder. <https://www.ncbi.nlm.nih.gov/books/NBK553166>, at 2 (emphasis added).

<sup>1649</sup> Lembke, “*Drug Dealer, MD*,” fn. 3, above.



assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA.<sup>1650</sup>

c. The Toyota-ization of Medicine

i. The majority of doctors today work in large integrated health care systems. During the 1990s and 2000s, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and operated by hospitals or integrated health delivery systems, and that number continues to rise.<sup>1651</sup>

ii. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, guidelines (*see* Joint Commission, §C.4.m, above), and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have “satisfied customers.” This too has contributed to the problem of overprescribing.<sup>1652</sup>

iii. These structural factors opened the doors, but the aggressive misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.

d. I have also written, in *Drug Dealer, MD*, about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact, they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own misleading statements regarding their dangerously addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor’s prescription have little or no risk of addiction or overdose.

e. An article published in *Science* in 2018 by Jalal, *et al.*, “Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979-2016,”<sup>1653</sup>

<sup>1650</sup> Lembke, “*Drug Dealer, MD*,” fn. 3, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinel/MedPage Today*. October 7, 2003, *see*

<http://www.medpagetoday.com/PainManagement/PainManagement/42103>, at p. 1.

<sup>1651</sup> Kocher R, Sahni N. Hospitals ‘ Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *N Engl J Med*. 2011;1790-1793, at p. 1791.

<sup>1652</sup> Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

<sup>1653</sup> Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science*. 2018. doi:10.1126/science.aau1184.

suggests that mortality data from numerous “drug-specific subepidemics” can be fitted to a smooth exponential curve during that time period. However, the authors note the “paradox” presented by these results, since the data combine mortality associated with subepidemics as disparate as heroin and fentanyl deaths in the northeastern United States with methamphetamines in the southwestern states.<sup>1654</sup> Accordingly, an after-the-fact fitting of 38 years of combined data to a smooth curve does not obviate the need to understand each subepidemic on its own terms. In the case of prescription opioids, factors relevant to that epidemic have been addressed throughout this report, and are summarized as follows:

- i. The apparent continuity of the overdose mortality rate curve in the Jalal *et al.* article, on closer inspection, shows a definitive rise above the smooth curve between 2001 and 2010, corresponding to the prescription opioid epidemic.<sup>1655</sup>
- i. This is further affirmed in Jalal’s most recent paper on the subject which acknowledged the likely causal role of prescription opioids in rising overdose mortality, under the heading, “**What is causing the exponential growth trajectory,**” stating that: “Over the past forty years, the dominant opioids have transitioned from crude plant-based drugs (heroin) to *pharmaceutical grade semisynthetic drugs (oxycodone)* to fully synthetic drugs (fentanyl and its derivatives). With these improvements in synthesis have come *improvements in purity, lower prices, and increased potency*. Conventional market forces may be at play, with *lower costs in product leading to expanding markets, increased use, and greater demand*. Improved technologies for communications and transport may also be altering the economics of drug use.”<sup>1656</sup> In other words, Burke and Jalal are explicit that prescription opioids are a *cause* of the exponential increase in overdose mortality, and that price and availability are key drivers.
- ii. A study by Segel *et al.* demonstrates that the prescription opioid epidemic that incited the broader opioid epidemic, has also contributed to the fourth wave of the epidemic involving a rise in sedative and stimulant overdose deaths.<sup>1657</sup>
- iii. The problem of addiction more broadly in society and culture today does not negate the significant role of opioids manufacturers and distributors in causing this epidemic. The misrepresentations of risks and benefits and the oversupply of prescription opioids through the

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<sup>1654</sup> *Id.* at p. 1.

<sup>1655</sup> *Id.*

<sup>1656</sup> Burke DS, Jalal H. Reply Commentary by Jalal and Burke. *International Journal of Drug Policy*. 2022;104:103674: 1-5, at p. 4. (emphasis added)

<sup>1657</sup> Segel, “Persistence and Pervasiveness”, fn. 1458, above, at p. 1.

distribution chain were essential contributing factors to the resulting epidemic.

- iv. Although forces may be operative to accelerate demand, such as despair, loss of purpose, and dissolution of communities, studies show that the ‘push’ of increased access to opioids has played a bigger role than the ‘pull’ of despair.<sup>1658</sup>
- v. Oversupply of prescription opioids is associated with increased opioid-related mortality. Approximately 86 billion oxycodone and hydrocodone pills were delivered to US pharmacies from 2006 to 2013 and per capita pill volume (“PCPV”) has been positively associated with opioid-related deaths (“ORDs”), so that “each one-pill increase in PCPV was associated with 0.20 additional ORDs within the following three years.”<sup>1659</sup> Griffith *et al.* further found that “even after accounting for various confounding factors, counties with particularly high PCPV experienced substantially more (16,436) ORDs than counties with below-median PCPV. On a national level, these excess deaths equate to approximately 11.1% of all ORDs recorded from 2006 to 2013”.<sup>1660</sup>
- vi. The harms of the opioid epidemic are urgent and ongoing. According to the Stanford-*Lancet* Commission: “Large numbers of US and Canadian people are still becoming addicted to prescription opioids each year, and most of those who die from heroin and fentanyl overdoses are previous or current users of prescription opioids.”<sup>1661</sup> The Commission’s opioid crisis model estimates that, in the absence of any intervention, an additional 1,220,000 fatal opioid overdoses will occur in the US between 2020 and 2029.<sup>1662</sup>

**15. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.**

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<sup>1658</sup> Ruhm, *et al.*, “Deaths of Despair,” fn. 1522, above.

<sup>1659</sup> Griffith KN, *et al.* Implications of county-level variation in US opioid distribution. *Drug and Alcohol Dependence*. 2021;219:1-7, at p.3.

<sup>1660</sup> *Id.* at p. 4.

<sup>1661</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 5.

<sup>1662</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 12.

- a. Primary prevention: Preventing new cases of the disease by limiting access to opioids, re-educating prescribers, and rebuilding communities devastated by the epidemic.
  - i. Opioids should not be prescribed as first line treatment for most forms of pain. Exceptions include cases of severe tissue injury, peri-operatively when multimodal analgesia is insufficient, and as palliative/end of life care.
    - A. For acute pain, the CDC guidelines recommend no more than 3 to 7 days of opioid treatment. Even within this general guideline, it is important to limit both the dose and frequency of administration of opioid drugs during the 3-7 day window, to minimize the increase in long-term use that has been documented following higher doses of opioids for acute pain, and to limit the diversion of unused pills.
    - B. First line treatment for pain should include non-opioid medications and non-medication treatment for pain (non-opioid medications, physical therapy, psychotherapy). The latter are especially important for the treatment of chronic pain.<sup>1663</sup>
    - C. There may be unusual instances when opioid medications can be used to good effect in the treatment of chronic pain; but even in this setting, avoiding daily use to avoid tolerance and dependence is recommended. Further, very close monitoring for the emergence of adverse medical consequences, including misuse and addiction, using objective criteria such as urine toxicology and database scrutiny, are essential components of a safe and effective treatment plan. Further, an exit strategy for cessation of opioid therapy is necessary, should risks outweigh benefits at any point in the treatment, in recognition that most patients will have become dependent and will taper with difficulty.<sup>1664</sup>
  - ii. Data on the impact of interventions to curb opioid prescribing have recently become available supporting the view that limiting opioid prescribing in a systematic way reduces prescription opioid-related overdose deaths without adversely compromising pain treatment.
    - A. Massachusetts had the first of its kind state-wide acute care prescribing limits and a required-check of the Prescription

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<sup>1663</sup> Delgado, *et al.*, “National Variation,” fn. 1464, above, at p. 389.

<sup>1664</sup> Dunn, *et al.*, “Opioid Prescriptions,” fn. 1560, above, at p. 86.

Drug Monitoring Programs (PDMPs) prior to opioid prescribing. As a result it reduced opioid prescriptions by 30%.<sup>1665</sup>

- B. The Department of Public Health determines mean and median quantity and volume of prescriptions for opioids, within categories of similar specialty or practice types. Prescribers who exceed mean or median will be sent notice.<sup>1666</sup>
- C. The law establishes a drug stewardship program to be paid for by drug companies that makes it easier for patients to safely dispose of unwanted and unused medications. Effective Jan. 1, 2017.<sup>1667</sup>
- D. The State of Massachusetts has launched core competencies for safe prescribing of opioids in the state's medical schools, community health centers, nursing, physician assistant, dental schools and schools of social work."<sup>1668</sup> Commensurate with decreases in opioid prescribing, Massachusetts has seen a decrease in opioid-related overdose deaths: "Opioid-related overdose deaths in Massachusetts have fallen steadily over the past three quarters even as the presence of fentanyl in overdose deaths reached an all-time high....Overall in 2017 there was a 4 percent decrease in opioid-related overdose deaths from 2016. The data also shows that the Commonwealth has experienced a 30 percent decline in opioid prescriptions since the launch of the Massachusetts Prescription Monitoring Program (MassPAT) in August 2016."<sup>1669</sup>
- E. A successful program in Chittenden County, Vermont achieved a 50% decline in opioid mortality through a multi-faceted program that included an increased capacity "hub" (the County) and increased number of physicians treating opioid addiction (the "spokes"); a Safe Recovery syringe exchange center and low-barrier sites for buprenorphine treatment; and

<sup>1665</sup> Sandoe, E., *et al.*, "Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic", Health Affairs Blog. (Oct. 2, 2018). <https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/>.

<sup>1666</sup> *Id.*

<sup>1667</sup> *Id.*

<sup>1668</sup> Massachusetts Department of Public Health Press Release, "Year Over Year Opioid-Related Overdose Deaths Decline in Massachusetts; Opioid Prescriptions Fall 30 Percent", August 24, 2018. *See* <https://www.mass.gov/news/year-over-year-opioid-related-overdose-deaths-decline-in-massachusetts-opioidprescriptions>, at p. 3 (emphasis in original)

<sup>1669</sup> *Id.* at p. 1.

support for a recent statute requiring such medications to be provided to prisoners with addiction treatment.<sup>1670</sup>

- F. As stated by the *Stanford-Lancet* Commission, “Contrary to fears that safer prescribing initiatives necessitate obliging long-term patients to taper opioids, more than 90% of the reduction in long-term prescription opioid use resulted from reducing the number of new long-term patients.”<sup>1671</sup>
- iii. As noted previously, an article in the *New England Journal of Medicine* in 2010 included the comment that prescription opioids are “essentially legal heroin” as well as a comment as to how the FDA should revise a Risk Evaluation and Management Strategy (REMS) for use of opioids, a FDA Advisory Board member stated, “We need to think about how we would construct a REMS if we were going to be marketing heroin.”<sup>1672</sup> I agree with these statements, since prescription opioids are as addictive as heroin and operate on the same neuro-circuitry in the same manner. Current REMS training is insufficient to educate prescribers about the risks of opioids. We need more comprehensive prescriber training on the evidence of benefits and harms with opioids for medical use, how to monitor patients taking opioids for medical use, how to taper patients off opioids, and how to intervene when a problem arises.
- iv. Medical and nursing schools across the country are beginning to implement addiction medicine curricula, an essential part of the reform process to combat this epidemic. I have led an initiative here at Stanford University School of Medicine to create our first ever addiction medicine curriculum since 2017, and I am involved in promoting similar initiatives across the country.
  - A. As explained at paragraph 26, above, I have been asked to “re-educate” doctors in many jurisdictions, to correct misinformation and provide accurate data on the significant risks and minimal benefits of opioid therapy, particularly for chronic pain. Such re-education is designed to reduce or eliminate over-prescribing of opioids, and thereby reduce or eliminate the panoply of ill effects that they cause

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<sup>1670</sup> City of Burlington, Mayor’s Office, Press Release, “Mayor Miro Weinberger and Community Partners Announce 50 Percent Decline in Opioid-Related Overdose Fatalities in Chittenden County in 2018 (Feb. 14, 2019), <https://www.burlingtonvt.gov/Press/mayor-miro-weinberger-and-community-partners-announce-50-percent-decline-in-opioid-related>.

<sup>1671</sup> *Stanford-Lancet* Commission, fn 17, above, at p. 23.

<sup>1672</sup> Okie, “A flood of opioids”, fn. 1223, above, at p. 1981.



- B. I testified at a White House symposium<sup>1673</sup> on the importance of educating health care providers on addiction treatment and safe prescribing. At that symposium, I suggested a school loan repayment program to incentivize health care providers to treat addiction in underserved areas after completing their training. This suggestion was taken up by Representative Clark and Representative Rogers as the Substance Use Disorder Workforce Loan Repayment Bill, which was included as a key provision in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, also known as the SUPPORT Act, passed September 28, 2018. Although the legislation was approved, there is yet to be a source of funding.
  - C. I am the Program Director for Stanford's Addiction Medicine Fellowship, a one-year fellowship to provide advanced training in addiction medicine. I also work on a national level to promote these fellowships, and was the inaugural president of the Addiction Medicine Fellowship Directors' Association (AMFDA).
  - D. I have authored articles on the importance of teaching addiction medicine to medical students, residents, and fellows, including "The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine" (Academic Psychiatry, 2018)<sup>1674</sup> and "Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum (Academic Psychiatry 2018).<sup>1675</sup> In these articles, I address the need for more robust training in the screening and intervention of patients with the full spectrum of opioid use disorders (including misuse and dependence). I further recommend increasing medical school hours of training in addiction medicine, including safe prescribing of controlled substances.
- v. Consider prohibiting the pharmaceutical industry from funding or influencing Continuing Medical Education (CME) courses for prescribers.

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<sup>1673</sup> The Addiction Medicine Foundation, "Congressional Briefing – Addiction Medicine: The Urgent Need for Trained Physicians" (Sep. 28, 2017), <https://www.youtube.com/watch?v=y6kBoQckmHw>.

<sup>1674</sup> Lembke A, Humphreys K. The Opioid Epidemic as a Watershed Moment for Physician Training in Addiction Medicine. *Acad Psychiatry*. 2018;42(2):269-272. doi:10.1007/s40596-018-0892-8.

<sup>1675</sup> Raber I, Ball A, Papac J, Lembke A, *et al*. Qualitative Assessment of Clerkship Students' Perspectives of the Topics of Pain and Addiction in their Preclinical Curriculum. *Acad Psychiatry*. 2018;42(5):664-667.

- A. The Stanford-*Lancet* Commission further recommends curbs to pharmaceutical industry influence on prescribers, regulators and the political process through, for example, curbs on the promotion of pharmaceutical products, the exposure of fraudulent advocacy groups and closing the so-called revolving door between the pharmaceutical industry and regulators.<sup>1676</sup>
- vi. Consider promoting CME education that explicitly eschews industry funds and influence, and providing academic detailing (unbiased, evidence based information for prescribers).
- vii. Earmark money to provide medical school, residency, and fellowship training in addiction treatment.
- b. Secondary prevention: limit progression of harm by helping patients on dangerously high doses come down or off of opioids, independent of whether they are addicted, and by implementing harm reduction strategies to mitigate the dangers of opioids.
  - i. To accomplish effective, safe, and compassionate opioid tapers in this country, we need funding to build de-prescribing clinics to provide treatment for opioid dependent patients. Where de-prescribing clinics are not feasible, we need to embed an interdisciplinary, chronic care treatment team inside of primary care to support deprescribing/opioid tapering. This chronic care team would consist of physicians, nurses, social workers, case workers, psychologists, and others trained to help patients manage the physically and emotionally taxing process of decreasing prescribed opioids. Primary care doctors, already overloaded with responsibilities, are unlikely to achieve successful tapers in opioid dependent, high dose legacy patients, without significant incentives and support. This will require an enormous investment of resources, as it is estimated that millions of Americans are dependent on opioids and suffering from or at heightened risk for adverse consequences.
  - ii. I worked with colleagues at Stanford to develop a protocol for helping opioid dependent patients compassionately and safely taper down or off of prescribed opioids: “The BRAVO Protocol.” The protocol has been adopted by the Oregon Pain Guidance, the Oregon Pain Task Force, and has influenced other opioid task forces around the country who are struggling with the problem of opioid dependent (but not addicted) chronic pain patients.<sup>1677</sup>

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<sup>1676</sup> Stanford-*Lancet* Commission, fn 17, above, at p. 11.

<sup>1677</sup> Oregon Health Authority Oregon Opioid Taper Guidelines Task Force Resources.

<https://www.oregon.gov/oha/PH/PreventionWellness/SubstanceUse/Opioids/Documents/taskforce/tapering-taskforce/2019-Opioid-Taper-Task-Force-Resources.pdf>.

- iii. We have created a free online continuing medical education course - “The BRAVO Protocol: How to Taper Patients Off of Chronic Opioid Therapy.” This course, created in conjunction with the Stanford continuing medical education office, teaches prescribers how to safely and compassionately taper opioids, something that is not currently taught in medical schools.
  - iv. As mentioned above (§A¶28), our tapering protocol was endorsed by the United States Department of Health and Human Services in 2019, and it became the subject of a Continuing Medical Education course in 2020. The course has also been positively featured in the lay press, highlighting that it features the first-person account of a patient who was, with support, able to taper off of opioids and experienced improved chronic pain as a result.<sup>1678</sup> We have created a companion page summarizing The BRAVO Protocol, which has gained wide informal distribution among prescribers. It summarizes the key learning points as below. (*See* BRAVO Protocol summary at Appendix V of this Report.) The bottom line is, helping patients to decrease or discontinue long term opioid therapy presents a challenging clinical scenario, especially in patients on high doses (greater than 80 MEDs), with moderate to severe chronic pain, and co-occurring mental health disorders (depression, anxiety, PTSD). For this type of complex chronic pain patient, the usual recommendation to decrease opioids by 10% of the starting dose every week frequently will not apply. These patients often need slower tapers on the order of 5-10% decreases or less every month. Expert consensus suggests the taper speed should be tailored to the individual needs of the patient. Some patients who have been on opioids for years to decades, may require *years* to taper their dose. With this complex chronic pain patient in mind, the BRAVO protocol outlines a safe and compassionate strategy to approach opioid tapering, while also maintaining a therapeutic alliance between the treatment team and each patient.
  - v. Other harm reduction strategies include increasing naloxone distribution, promoting clean needle exchanges, improving patient education regarding safe medication storage and appropriate disposal of excess medications, and increasing public awareness of poison center services.
- c. Treatment
- i. We need a robust infrastructure to treat addiction, both within and outside the traditional sources for medical care. Such an infrastructure does not currently exist. Instead what we have are siloes of care with

<sup>1678</sup> Parloff R. Tapering off long-term Rx opioids: a first-hand account, Opioid Institute. (Oct. 15, 2018), <https://opioidinstitute.org/2018/10/15/tapering-opioids-lembke/>. (last accessed January 15, 2019)

limited and contingent funding, or treatment centers accessible only by the rich.

- ii. Addiction treatment should be offered within every hospital, clinic, emergency room, jail, drug court, etc., across America. “Meeting patients where they are” has become a mantra for the field. Patients with this complex behavioral illness are more likely to engage in treatment when they are offered treatment in settings where they are frequently found, like in hospitals, emergency rooms, jails, and even in settings where they might be using drugs (such as at the site of first responders, clean needle exchange sites, safe consumption sites, etc.).
- iii. An effective addiction treatment infrastructure should be based on evidence-based treatments for addiction, including buprenorphine, methadone maintenance, and naltrexone. Opioid agonist therapy (buprenorphine or methadone maintenance) has one of the most robust evidence bases of any addiction treatment. Multiple placebo controlled trials over many decades have demonstrated the efficacy of opioid agonist therapy in the treatment of opioid use disorder.<sup>1679</sup>
- iv. Studies have shown that treatment with buprenorphine and methadone reduced the relative risk of opioid overdose death by 34-38% even if the treatment was not continued.<sup>1680</sup> Similarly, medications to treat opioid use disorder (MOUD) (buprenorphine, methadone, ER naltrexone) have been shown to protect against repeat overdose, with a 76% reduction in risk of subsequent non-fatal overdose.<sup>1681</sup> However, despite guidelines recommending MOUD, only 10.7% of patients received MOUD in the year after an index overdose<sup>1682</sup> and only approximately 1 in 5 adults with past-year OUD received any MOUD.<sup>1683</sup>
- v. In a promising development, in 2023 the US Congress removed the federal requirement for a special waiver and other restrictions on prescribing buprenorphine for the treatment of opioid use disorder, allowing all current DEA registrants to prescribe buprenorphine for their patients.<sup>1684</sup>

<sup>1679</sup> Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. *Lancet*. 2012;379(9810):71-83, at p. 78.

<sup>1680</sup> Heimer, “Receipt of opioid use disorder treatment”, fn. 1591, above, at p. 1.

<sup>1681</sup> Tipping, “Medications for opioid use disorder”, fn. 1590, above, at p. 8.

<sup>1682</sup> *Id.*, at p. 7.

<sup>1683</sup> Jones CM, *et al.* Use of medication for opioid use disorder among adults with past-year OUD in the US, 2021. *JAMA Network Open*. 2023;6(8):1-4, at p. 3.

<sup>1684</sup> Substance Abuse and Mental Health Services Administration (SAMHSA). Waiver Elimination (MAT Act).(last updated Oct. 10, 2023) <https://www.samhsa.gov/medications-substance-use-disorders/waiver-elimination-mat-act>

- vi. Addiction is a chronic relapsing and remitting disorder, requiring a chronic care model and a team based approach, including a peer recovery coach, care coordinator, behavioral health specialist, licensed counselor, and a primary care professional.<sup>1685</sup> One way to address this problem within our current health care system, is to co-locate behavioral health specialists within primary care, or create a hub and spoke model with specialty clinics providing support to primary care clinics. A concurrent strategy is to build Centers of Excellence for Addiction Treatment at every major medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.
- vii. As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT (Medication-Assisted Treatment). Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT resources possible, as quickly as possible, and should maintain this level of treatment long-term, as contemplated in the proposed abatement plan.
- viii. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.
- ix. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.
- x. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care.

#### **D. Conclusion**

Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. One of the biggest risk factors for addiction is simple access to addictive drugs. When supply of an

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<sup>1685</sup> “The Addiction Recovery Medical Home As An Alternative Payment Model,” Health Affairs Blog, December 12, 2018. DOI: 10.1377/hblog20181211.111071. *Heal Aff Blog*. doi: 10.1377/hblog20181211.111071, at p. 3.

addictive drug is increased, more people become addicted to and suffer the harms of that drug. The Defendants' conduct in promoting increased supply and widespread access to prescription opioids, including through misleading messaging, has resulted in an epidemic of opioid addiction and overdose death. Increased supply contributed to more pain patients becoming addicted to opioids, including those who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect). Increased supply contributed to more pain patients and newborns becoming dependent on opioids, increasing their risk for opioid-related morbidity and mortality (The Dependence Effect). Increased supply contributed to more diversion of prescription opioids, causing a dramatic increase in the widespread availability of opioids to persons for whom they had not been prescribed (The Tsunami Effect). The increased supply of prescription opioids through licit and illicit sources resulted in a prescription opioid epidemic in the United States. Others bear some lesser responsibility for the opioid epidemic. However, today's opioid crisis would not have occurred without the paradigm shift encouraged by the Pharmaceutical Opioid Industry, whose actions resulted in the overprescribing and excessive distribution and dispensing of prescription opioids. In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."<sup>1686</sup>

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted and will accomplish the following: prevent new cases of addiction, dependence, and death (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment).

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<sup>1686</sup> Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.



*Lembke Report*

*Confidential — Subject to Protective Order*

**Exhibits to this Report:**

Attached as Exhibit A is a copy of my current curriculum vitae and a list of all publications authored by me in the past 10 years.


Attached as Exhibit B is a list of data or other information considered by me in forming the opinions expressed herein.

Attached as Exhibit C is a statement of my compensation for services performed in this case.

Attached as Exhibit D is a list of all cases in which I have testified as an expert at trial or by deposition during the past four years.

Pursuant to 28 U.S.C. S 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on: February 7, 2024

  
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**Anna Lembke, M.D.**

# Anna Lembke, M.D. Report

## APPENDIX I

### Misleading Promotional Messages

I.A: Purdue Pharma

I.B: Teva/Cephalon

I.C: Janssen

I.D: Endo

I.E: Allergan

**Appendix I.A: Purdue Pharma****Purdue Misleading Messaging****A. Benefits of Opioids Not Supported by Reliable Scientific Evidence****1. *Myth: Opioids are effective for chronic pain***

- “[W]e now know that many patients with chronic, nonmalignant pain respond very well to opioids and that, contrary to our teaching, addiction is very rare and possibly nonexistent as a result of treating such patients with opioids. The barriers to vastly improved treatment for hundreds of thousands of people in pain, are simply the misinformation and prejudice of doctors, pharmacists and regulatory bodies.” Purdue Physicians’ Pain Management Speakers Training Program, April 18-20, 1997. PKY181654940 at 4966.

**Comment:** This quote summarizes the essential message promoted initially by Purdue and subsequently by other opioid sellers: that opioids are effective for chronic pain, and that “addiction is very rare and possibly nonexistent,” as a result of such treatment. With some variation, the promotional messages detailed in this appendix follow those two themes. As to the claim of efficacy for chronic pain, there was not then, and there has never been, reliable evidence to support the claim; as to the assertion of “rare” addiction risk with opioid therapy, there were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began the aggressive marketing campaign that omitted any reference to those data, and numerous additional, subsequent studies consistent with the earlier results.

- “Opioid analgesics are indicated for moderate to severe pain that cannot be relieved with other agents. Opioids are effective, easily titrated, and have a favorable benefit-to-risk ratio. Large doses of opioids may be needed to control pain if it is severe, and extended courses may be necessary if the pain is chronic. Tolerance and physical dependence are normal physiologic consequences of extended opioid therapy and must not be confused with addiction. Patients and family members must be educated regarding the difference between tolerance, physical dependence, and addiction. Patients with chronic, severe pain must not consider themselves addicts because they are being treated with opioids. Concerns about addiction should not prevent the appropriate use of opioids. McPhee JS, Schroeder SA. In Lange’s Current Medical Diagnosis Treatment, 1996 p 13.” Purdue Physicians’ Pain Management Speakers Training Program, April 18-20, 1997. PKY181654940 at 4969.

**Comment:** This quote builds on the basic message (above) by recommending titration to “large doses,” without disclosing that risk goes up as dose goes up; and

by downplaying the significance of physical dependence, which is a significant medical problem.

- Presentation by Dr. Melvin Gitlin entitled “The Use Of Opioids in the Treatment of Chronic Non-Cancer Pain” at the Purdue Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5155-5157 in which he states, “Historically the use of opioids for pain management has been influenced less by scientific data than by subjective attitudes, personal opinion and legislative regulatory influence....Regulatory agencies in the United States are increasingly acknowledging this; some are seeking to reassure clinicians that the legitimate use of opioids should not engender fear of reprisal.... A well designed, double-blind, randomized cross over trial utilizing patient controlled analgesia morphine studied opioid responsiveness in chronic pain. The authors demonstrated that although nociceptive pains exhibited a better analgesic response than did neuropathic pain, approximately 50% of patients with neuropathic pain did show a good or better analgesic response to the opioid.” The study to which Dr. Gitlin refers, by Jadad, *et al*, “Morphine responsiveness of chronic pain”, Lancet 1992, is not in fact a study of the use of long term opioid therapy in the treatment of chronic pain. Rather it is a study of one-day dosing of opioids in a population of patients with chronic pain, answering an entirely different question than whether opioids work for the treatment of chronic pain. Treating chronic pain patients for a day is not comparable to treating the same population with opioids on a long-term basis.
- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5168, in which she states “opioid analgesic drugs are effective for moderate to severe pain,” under the heading “AGS Clinical Practice Guidelines for Chronic Pain,” without clarifying the lack of reliable evidence for the use of opioids in the treatment of chronic pain.

## 2. ***Myth: Opioids are first-line treatment for all types of pain***

- "Opioids are our strongest and safest medications for most disablingly-severe pain. Our obligation is to consider them in all such cases." “Control of Pain: Every Person's Right ” Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545. Part of a Purdue sponsored speakers training program in Beverly Hills, CA.
- "Opioids for Neuropathic Pain--All patients & all types of pain are opioid responsive. There can be variation in the degree of response. May need to titrate to adequate analgesia but intolerable side effects; change opioids. Nociceptive (visceral, somatic) and neuropathic pain responsive to opioids." HSS Training

Presentation, August 25, 2000. PKY180435433 at 5565. Purdue sales reps are called "Health Systems Specialists" (HSS) and this was a Purdue Training Presentation for Reps and District Managers.

**Comment:** The quotes above do not distinguish between acute pain and chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

### 3. *Myth: Opioids are safer than the alternatives*

- "We now know that in appropriately selected patients, opioids have a low morbidity (perhaps less than NSAIDs), and a low addiction potential. Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5092.
- Presentation by Dr. Mary Stegman entitled "Pain Management in the Elderly Patient, Special Considerations," for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5166, in which she highlights the risks of acetaminophen, including renal and hepatotoxicity, and in which she claims opioids are "safer than NSAIDs," but never discusses the absolute or relative risks of opioids.

**Comment:** There was no reliable evidence to claim that opioids were "safer, or "perhaps" safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse events. (Solomon study); also, the Krebs study (SPACE trial) found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

### 4. *Myth: Opioids improve function and quality of life*

- "In studies of patients with non-malignant pain...Rapid reduction in pain intensity over the first 24 hours; By day three, patients had achieved 94% of their total pain reduction; Patients reported improved ability to sleep, walk, perform normal work, *get along* with other people, enjoy life." OxyContin Launch Plan, September 27, 1995. PURCHI-003286781 at 6804.

- "Provides quality of life benefits-relative to placebo, OxyContin significantly decreased pain, and improved quality of life, mood and sleep." OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450 at 5455
- "Controlled Release Opioids - Cognitive Effects: decreases anxiety, decreased hostility, no declines in cognitive function, improved psychomotor speed, improved sustained attention." Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5175.
- "Benefits of Long-Acting Opioids -- Better pain reduction with better function. Improved sleep. Reduced anxiety. Reduced hostility. No impairment of cognitive function. Improved psychomotor speed. Improved sustained attention." HSS Training Presentation, August 25, 2000. PKY180435433 at 5635.

**Comment:** The statements above are misleading because they were intended to justify long-term OxyContin therapy for chronic pain, based on short-term studies.

**5. *Myth: Not using opioids is tantamount to undertreating pain, is hence immoral, and may make pain worse in the long run, and risks reprisal from regulatory bodies.***

- Presentation by Dr. Neil Irick entitled "Can We Justify Undertreating Pain?" for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999 in which he invokes The Joint Commission Requirements as justification and persuasion: "The patient's right to pain management is respected and supported," "Pain as the 5th vital sign," "Statement of patient rights available to all..." Dr. Irick also states, "Remember: resolve that no patient should suffer needlessly, listen to the patient, believe the patient, document, be your patient's advocate." PKY181655140 at -5150 and 5152.
- Presentation by Dr. Mary Stegman entitled "Pain Management in the Elderly Patient, Special Considerations," for Purdue's Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at -5161 in which she states, "In 2000, JACHO will demand pain TX [treatment]."
- "Based on new literature on the Pathophysiology of pain, it is important to PREVENT the pain as opposed to simply treating the pain. Otherwise, you could have patients develop what is referred to as 'Wind up' which can lead to a complex pain syndrome. Let's say you had a patient present with low back pain from lifting heavy boxes. When that patient lifted the boxes and the injury occurred, the C fibers in his body were stimulated and started firing pulses basically like a strobe light. Those fibers synapsed with the secondary neurons and carried the pain signals to the brain. Think of the secondary neurons like the



aperture of a camera, except that instead of the aperture closing when that strobe light hits it, the aperture actually opens. The more light/or stimulus that spills through the aperture, the greater the sensation of pain. So, what happens is even though that stimulus may be diminishing, the threshold for pain has been lowered, and the number of signals have actually increased. This whole process starts a CASCADE OF EVENTS because once these signals are recognized on a consistent basis, they turn on the NMDA receptors which then release prostaglandins and nitric oxide initiating the ENTIRE chain of events again in the adjacent neurons. And what that does is lowers the threshold for pain again, and they start firing spontaneously. UNTIL these pain signals can be turned off the patient will remain in this 'wind up mode' and could develop a complex pain syndrome." HealthSouth Pain Management Plan, April 19, 2001. PKY181246683 at 6851. Document is part of "OxyContin Files (HD)" which includes presentations and papers made by Purdue to HealthSouth re: adoption of their new pain management plan.

**Comment:** The statements above were misleading and detrimental to patients, for the following reasons. First, these statements represent the opioid sellers' efforts to increase prescribing by instilling fear of reprisal from the State Medical Boards and/or The Joint Commission, as well as patients demanding opioids and complaining about their care. The message to prevent pain before it happens was leveraged to support the controversial idea that untreated pain can lead to centralizing pain disorders, which would not only leave acute pain untreated, but also risk a life-time condition if a centralizing pain disorder were to develop. Even if this centralizing pain phenomenon exists, opioids are the worst possible treatment, because these disorders are closely linked to depression and addiction, and the risks for such conditions are exacerbated by opioid therapy.

## B. Risks of Opioids Understated

### 1. *Myth: Addiction is rare*

- "Realize that drugs and doctors do not cause drug addiction. Admit that withholding pain medication can be deleterious. Admit that true addiction is much less of a problem than presumed." Purdue Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5080.
- Presentation by Dr. Melvin Gitlin at the Purdue Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5156, in which he states, "Persuasive evidence that the use of opioid presents either a risk to the health of the individual or to society is lacking. Similar prejudices had been advocated to impede the opioid treatment of patients with malignant pains and are being overcome."

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at PKY181655169, in which she states “Myth: Opioids create addicts” outlining a study of 10,000 burn patients, 0 patients (0.00%) were addicted; another study of 25,000 patients, only 7 patients (0.03% patients) were addicted, concluding “Forget That Excuse!” As discussed in my Report, the studies to which she refers are non-representative samples in studies ill-designed to assess for misuse and addiction.

**2. *Myth: The problem is the ‘addicts,’ not the drug***

- “Are Opioids Always Addictive? No! Watch out for cherry syrup addicts! Opioid addicts should not be given opioids without careful consideration of the circumstances.” Accredited Pain Management Program for the Educator, August 3-6, 2000. PKY180775599 at 5650.

**Comment:** By using the term “cherry syrup addicts,” the author is presumably referring to patients with opioid addiction getting treated with methadone in liquid form from a methadone maintenance clinic. This pejorative usage is typical of the ways in which Purdue labeled and stigmatized people with opioid use disorder, and promoted the idea that by separating opioid addicted persons as a distinct population, the remaining patients could be prescribed opioids without risk.

- “Molecules don’t hook patients, patients with psychopathology take drugs to be fixed. Addicts want medications for wrong reason, trying to get high, not to have less physical pain.” Accredited Pain Management Program for the Educator, August 3-6, 2000. PKY180775599 at 5652.

**Comment:** This statement perpetuates the myth that ‘addicts’ are a separate category from ‘legitimate’ pain patients. The reality is that legitimate pain patients can and do get addicted through an opioid prescription.

**3. *Myth: No dose is too high; optimal dose is determined by titrating upwards until analgesia***

- “No ‘ceiling’ to analgesic efficacy - may be titrated upward as necessary. With full agonists, such as oxycodone, ‘effectiveness with increasing doses is not limited by a “ceiling.”’” OxyContin Launch Plan, September 27, 1995. PURCHI-003286781 at 6804.
- “No maximum daily dose or ‘ceiling’ to analgesic efficacy. May be titrated every 1 to 2 days, if necessary. Common opioid side effects may be effectively managed- many, except constipation, diminish over time for most patients.”

OxyContin Advertising and Black Box Warnings, June 15, 1998. PKY180625450 at 5452.

- Presentation by Dr. Mary Stegman entitled “Pain Management in the Elderly Patient, Special Considerations,” for Purdue’s Physician’s Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5172, in which she states “Titrate to effectiveness not to milligrams.”
- “There are no standard opioid doses. Patients experience their pain uniquely. Dosages not consistent due to individual variations in pain intensity mechanisms of action. Patients need doses that relieve or modify the pain without toxicity. Milligrams Just Don’t Matter...Milligrams are not the issue, pain control and absence of toxicity are the issues.” Accredited Pain Management Program for the Educator, August 3-6, 2000. PKY180775599 at 5647.

**Comment:** The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death.

**4. *Myth: Dependence is not a significant problem and is easily reversible***

- “Now, when was the last time that you took a patient off insulin because their blood sugar had gotten to normal? Do you taper your patients off their antihypertensive when their blood pressure gets to normal? In primary care our assumption is that we’re going to be treating people with chronic diseases for long-term, so why don’t we do that with pain patients?” “Legal and Ethical Issues Affecting Pain Management”, © 2001 a “Free CME” course “supported by an education grant from Purdue Pharma” and distributed by FamilyPractice.com and Purdue. PKY180769094 at 9123,9095

**Comment:** Comparing opioids to insulin is a false analogy because insulin does not cause diabetes; whereas exposure to opioids causes opioid dependence, and in a subset, opioid addiction.

- “Addiction is a behavioral disorder of ‘compulsive drug use, despite harm.’ This has not been recorded as a result of the medical use of opioids. Opioids do cause physical dependence, i.e. there is a brief, flu-like withdrawal syndrome on suddenly stopping them. But this is not addiction, it is not dangerous and is easily avoided by tapering opioids over about 2 weeks. (By contrast, the withdrawal syndrome for benzodiazepines can be very dangerous, and very prolonged. Preventing it may require tapering over a period of several months.)” Purdue Physicians’ Pain Management Speakers Training Program, April 18-20, 1997. PKY181654940 at 4966.

- Presentation from Dr. Neil Ellison at Purdue's Physicians' Pain Management Speakers Training Program in San Antonio, Texas on April 19, 1997: "Physical dependence will occur in most patients regularly taking opioids for prolonged periods of time (usually greater than several weeks); however, if the cause of the pain is relieved, these patients can safely and rapidly be withdrawn completely by fractionating (usually by 1/3-1/2 their doses daily or every other day). The patient can usually discontinue completely without withdrawal symptoms..." PKY181654940 at 4950.

**Comment:** Dependence and tolerance are serious physical conditions in themselves; they also lead to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering.

**5. *Myth: Tolerance is rare - respond with higher dose***

- "(Despite different findings in experimental animals,) a remarkable phenomenon is observed in the clinical setting. Loss of analgesia rarely occurs in patients with stable pain syndromes. Patients without progressive disease...typically achieve stable dosing that extends for a prolonged period. When the need for dose escalation occurs, an alternative explanation, typically worsening of the underlying disease, can usually be identified." Physicians' Pain Management Speakers Training Program, April 18-20, 1997. PKY181654940 at 4969, quoting Portenoy RK. In "Pain Management: Theory and Practice," ed Portenoy & Kanner, FA Davis Company, 1996: Chapter 11, p255.
- "Tolerance is defined as the need for increasing doses of medication to maintain the same effect. This is easily and reliably produced in animal models, yet is rarely seen in humans. In fact, in the case of cancer pain, what has thought to be tolerance has been shown to typically be disease progression necessitating the need for increased opioids to maintain comfort." Purdue Physicians' Pain Management Speakers Training Program, presentation by David Haddox, April 18-20, 1997. PKY181654940 at 4962.
- "Although tolerance may occur in some cases, generally patients become tolerant to bothersome side effects more so than to analgesic effects. Evidence from cancer studies suggests that when patients clinically stable on a certain opioid dose, request a dose escalation, it may be more related to progression in their disease than to tolerance." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5092.

**Comment:** Tolerance is not "rare" in humans. It is common. Tolerance leads to increased dosage and increased risk.

**6. *Myth: Pseudo-addiction – respond with more opioids***

- "[I]n the setting of undertreated pain, some patients develop aberrant behaviors that may be quite similar to those associated with addiction. When pain is relieved, the behaviors cease and opioids and other drugs are used responsibly." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5100.
- Types of Pseudoaddiction Behavior: "Hoarding; Concern about supply; May be going to multiple physicians and pharmacies; Drug-seeking behaviors common; First described in cancer patients." Physicians' Pain Management Speakers Training Program, March 20-22, 1998. PKY181655057 at 5081.
- "Pseudoaddiction: appropriate drug seeking behavior demanding doses before they are scheduled; viscous cycle of anger, isolation, and avoidance leading to complete distrust. Weissman DE, Haddox DJ. *Pain* 1989;36:363-6. Increase the opioid dose by 50%, assure that breakthrough doses are available; complaints resolve when analgesia is established." Physician's Pain Management Speakers Training Program, November 5-7, 1999. PKY181655140 at 5208. Haddox is now a Purdue Pharma VP of Health Policy. *See* Haddox ResearchGate Profile page at <[https://www.researchgate.net/profile/J\\_Haddox](https://www.researchgate.net/profile/J_Haddox)> Accessed on January 25, 2019.
- "Pseudoaddiction Relative to Psychiatric Pain Consultations--Involves appropriate attempts to obtain medication to relieve pain. "Clock watching" behavior is indicative of under treatment of pain. We should believe patients unless evidence proves otherwise. Consider 50 to 100% dose increase to see if the behavior changes." Accredited Pain Management Program for the Educator, August 3-5, 2000. PKY180775599 at 5649.
- "[T]he more the patient insists on the need for stronger pain medicine, the more likely we are to withhold analgesia, on the grounds that this insistence shows 'substance abuse,' for which the treatment is abstinence from the 'offending substance'. We equate this 'drug seeking behavior' with addiction, and use it to justify further undertreatment or even complete withdrawal of analgesics. This further reinforces the patient's desperate pursuit of pain relief. If this leads to manipulateness or frank deceit, the misdiagnosis of addiction is reinforced. Not only the doctors, but also the patient and family may conclude that the problem is drug addiction. This is called 'pseudo-addiction,' a term first defined by Weissman and Haddox." "Control of Pain: Every Person's Right" presentation, Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545.
- "The distinction can usually be made quite simply. For a period of about a week, prescribe a substantially increased dose of opioid, preferably with a range of doses so that the patient can explore the optimum dose. The aim is to challenge

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the patient's ability to shed drug-seeking behavior when adequate analgesics are available. Every day the patient records pain level, activities tolerated, and total pills taken. After a week, he/she brings the record to the physician, along with remaining pills. Ideally the partner should come also. If the problem is pseudoaddiction, the patient will be visibly more comfortable and refreshed; the partner will corroborate the patient's account of improved activity tolerance; the daily pill count will be medically credible; and the remaining pill count will fit with the record. None of the aberrant behaviors listed above will have occurred: drug-seeking behavior has been extinguished at a stroke." "Control of Pain: Every Person's Right" presentation, Pain Management Speaker Training Program for Physicians, May 5-7, 2000. PKY180170528 at 0545.

**Comment:** As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.



**Appendix I.B.: Teva/Cephalon****Teva/Cephalon Misleading Messaging****A. Benefits of Opioids Not Supported by Reliable Scientific Evidence****1. Myth: Opioids are effective for chronic pain**

- “Opioid analgesics are another important class of medications that are very effective pain relievers. As mentioned before, they may also be called ‘narcotics.’ Unfortunately, this term is used by law enforcement to refer to drugs that are abused. Cocaine and heroin are called narcotics even though they are very different kinds of drugs. Calling opioid analgesics ‘narcotics’ reinforces myths and misunderstandings as it places emphasis on their potential abuse rather than on the importance of their use as pain medicines.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0514) The APF Guide discussed here and below was produced with the financial support of Cephalon and Purdue. (TEVA\_MDL\_A\_01090496 at -0499) KOL’s Scott Fishman and Russell Portenoy were named as physician reviewers and members of APF’s Board of Directors. (TEVA\_MDL\_A\_01090496 at -0501) Fishman and Portenoy also provided testimonials for the APF Guide, calling it a “must have” and “a very good resource” for chronic pain patients. (TEVA\_MDL\_A\_01090496 at -0579)

**Comment:** This quote summarizes the essential message promoted by Teva/Cephalon in a patient-facing document that promoted misleading messages under the guise of education. The authors describe non-opioid medications such as Tylenol and NSAIDs as “effective for mild to moderate pain,” but never as “very effective pain relievers,” a phrase reserved for opioids. Indeed the sections on NSAIDs and Tylenol emphasize the risks of these drugs. By contrast, when the authors detail opioids, the risks are underplayed, as in this statement in which heroin is called a “very different kind of drug,” even though the only difference between heroin and morphine is two acetyl groups, and prescription opioids are as addictive as heroin. Heroin and morphine are very similar drugs, yet are portrayed here as different to mislead readers as to the addictive potential of prescription opioids.

- “Despite the great benefits of opioids, they are often under-used. For a number of reasons, providers may be afraid to give them and the public may be afraid to take them. Some feel opioids should not be used to treat persistent pain except in persons who are dying. Others are concerned that the average person will become addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem is the increase in abuse of prescription drugs in the U.S. Persons with addictive

disease (in the past, the term ‘addicts’ was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them ‘on the street’ for profit.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0514-5)

**Comment:** The authors claim “great benefits of opioids.” In fact, there is no reliable evidence that opioids are effective treatment for chronic pain, or what authors here describe as “persistent pain.” Further, there is abundant evidence that opioids taken long term (greater than 3 months) incur considerable and life-threatening harms. Yet the authors suggest that “confusion and hesitation” on the part of prescribers is unfounded. They then go on to suggest that the current opioid crisis is a result of “addicts,” a stigmatizing term they use for supposed historical clarification, to imply that “addicts” are the source of the current opioid epidemic. In fact, increased access to opioids through the Defendants’ misleading marketing is the primary culprit, making the public more vulnerable to opioid addiction.

## 2. Myth: Opioids are first-line treatment for all types of pain

- “Opioids are an essential option for treating moderate to severe pain associated with surgery or trauma, and for pain related to cancer. They may also be an important part of the management of persistent pain unrelated to cancer. These medicines block pain messages in the body, but they also affect the way we feel about our pain and help us better tolerate it. Our body produces natural opioids (endorphins) as part of its survival response to danger and injury. Because the medications of this class work in the same way as endorphins, they work very well in blocking pain.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0514)

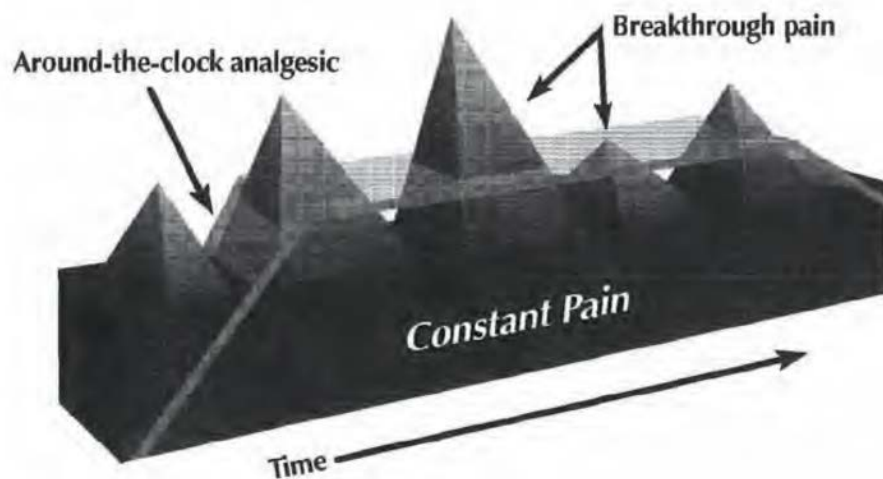
**Comment:** By calling opioids an “essential option,” the authors are suggesting that opioids are necessary to treat different types of pain. By introducing the concept of “natural opioids,” the authors are further trying to make a link between prescription opioids and something that is “natural” and thereby safer or necessary. Again they introduce the statement “they work very well in blocking pain,” to suggest their superiority compared to other pharmacologic strategies. In fact, head-to-head trials show that opioids are no better than Tylenol in the treatment of chronic pain, and incur more risks. Further, these statements do not distinguish between acute pain and chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there is no reliable evidence of efficacy for chronic, non-cancer pain. It is misleading to make a blanket statement of efficacy without making this distinction clear.

- “Targeting (APM, PM&R, RHU, N, ONC, PCP)” in sales presentation. A Manager’s Perspective on Actiq (TEVA\_MDL\_A\_09062111 at \*13, produced natively)

**Comment:** Note here how marketing materials targeted many types of pain and pain providers, including “PCPs” [Primary Care Physicians], contributing to the paradigm shift away from using opioids rarely in specialty care, to using opioids as first line treatment in primary care.

**3. Myth: Breakthrough Pain is a distinct clinical phenomenon that should be treated with opioids (rather than an artifact of tolerance and withdrawal in patients on long-term opioids).**

- “Breakthrough Pain. Breakthrough pain occurs on a background of otherwise controlled persistent pain; it is distinct from uncontrolled pain. Breakthrough pain is described as a transitory exacerbation or flare of moderate to severe pain in patients with otherwise stable persistent pain who are receiving chronic opioid therapy. In one study, the median duration of breakthrough pain was about 60 minutes. Breakthrough pain tends to be the most intense pain. Figure 6 illustrates this type of pain. [Payne, 2007, S3; Portenoy, 2006, 586; Davis, 2004, 629.]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0334). Figure 6 is reproduced below:



- “Fentanyl is also available in a lozenge. In this formulation, it has a quick onset and short duration of effect that makes it especially useful for the

treatment of ‘breakthrough’ pain.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0516)

- “Breakthrough pain is often managed by adding a medication in addition to the drug used for the persistent pain. [Payne, 2007, S4-S5; Duragesic, 2008, 1]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0335)
- “Third, frequent pain reassessment will help gauge the effectiveness of analgesic therapy. Assessment may help health care professionals choose more effective agents, titrate the dose or dosing interval appropriately, check the usefulness of the current route of administration, manage side effects, and assess the need for more effective breakthrough pain medication alongside the around-the-clock medication. [Carver. 2005, 10-11; McCarberg, 2007, S8]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0341)
- “ACTIQ is fentanyl in a unique oral transmucosal delivery system that provides the most rapid onset of analgesia of any non-invasive opioid formulation available which makes it the ideal agent for BTP or rapid onset pain, such as BTCP.” 2005 ACTIQ Marketing Plan (TEVA\_CAOC\_00759630 at -9675) (ACTIQ 2005 Positioning Statement, bolded in original)
- “2005 Key Marketing Issues and Strategies: The overall marketing strategy for 2005 will continue to build on the platform developed in previous years, which will be to raise awareness of BTCP and ACTIQ and differentiate ACTIQ from its competitors by educating clinicians about the core product benefits (rapid onset of analgesia, portability, convenience and patient controlled administration). The key marketing issues facing ACTIQ in 2005 that must be addressed include providing the sales force with effective tools as well as providing them with optimal messages for key targets; ensuring a smooth transition to sugar free ACTIQ; increasing awareness in assessing and treating BTCP; and addressing the fears and concerns surrounding opioids. Also, growing managed care issues must be addressed as well as increasing and improving Key Opinion Leader (KOL) relationships.” 2005 ACTIQ Marketing Plan (TEVA\_CAOC\_00759630 at -9633)
- “The goals are to maximize ACTIQ sales until patent expiry with focused sales efforts on specific targets and to ensure that any efforts toward establishing BTP can also be leveraged for OVF” [Teva OraVescent® containing fentanyl product]. 2005 ACTIQ Marketing Plan (TEVA\_CAOC\_00759630 at -9674)

**Comment:** Teva/Cephalon promoted the idea of “breakthrough pain” as a physiologic phenomenon, when in fact it is a made up term to explain the loss of opioid efficacy when taken long term, due to tolerance and

withdrawal. Promoting the idea of breakthrough pain as a legitimate medical phenomenon was advantageous for Defendants, because they could then promote their products as “treatment” for breakthrough pain. Actiq and Fentora were aggressively promoted as treatment for breakthrough pain.

**4. Myth: Not using opioids is tantamount to undertreating pain, is hence immoral, and may make pain worse in the long run.**

- “Obviously, it is very important to get the facts about these effective and powerful pain medicines because their under-use has been responsible for much unnecessary suffering. Those affected by pain, providers, patients and family alike, need to be well-informed to be sure that myths and misunderstandings do not get in the way of effective pain control.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0515)

**Comment:** Such statements are misleading and detrimental because they suggest to patients that doctors who are not prescribing opioids are not doing their job and indirectly causing suffering by withholding opioids. In fact, withholding opioids to a person in pain may be shielding them from long-term harms. Further, this fact has been known well before Defendants launched their misleading marketing campaign. A paper published in a peer reviewed medical journal in 1954 had this to say about prescribing opioids for pain, “Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures.” Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA*, 1954:684-691, at p. 690.

- “Physicians often undertreat pain due to a lack of education about pain. This results in an inadequate pain assessment and less than optimal treatment, such as use of nonsteroidal analgesics for severe pain.” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0350)

**Comment:** This statement suggests that not prescribing opioids is tantamount to not treating pain, ignoring the fact that even limited exposure to opioids is risky, and that many studies show comparable efficacy between opioids and other forms of pain treatment, with much less risk for non-opioid medications.

**B. Risks of Opioids Understated****1. Myth: Addiction is rare**

- “Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed... [Willis, 2007, 261- 262; AACPI, 2004, 6-7]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0346)
- “Patients can also inhibit therapy by refusing to take pain medications or by taking them inappropriately. Patients may hear descriptions of physical dependence about certain medications (opioids) and fear the stigma or behaviors they associate with drug addicts - behaviors that are not common in patients without previous history of addiction. Patients may believe that analgesics should be ‘saved’ until the end of life so that they are effective then; patients may need reassurance that an appropriate dosage of opioid will be available as pain increases, and they need not suffer now to avoid analgesic tolerance in subsequent disease stages. [Carver, 2005, 10-11, Gunnarsdottir, 2003, 426, Willis, 2007, 261]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0345)
- “Pain appears to reduce the euphoric effects of opioids, so people taking opioids to manage their pain may be at a lower risk for addiction. [APA, 2005, 2]” Fentora Introduction to Pain (TEVA\_MDL\_A\_00890305 at -0355)
- “Less potential for abuse” in sales presentation A Manager’s Perspective on Actiq (TEVA\_MDL\_A\_09062111 at \*10, produced natively)

**Comment:** The authors misleadingly convey that the risk of opioid misuse and addiction is low if patients with pain are prescribed opioids by their doctors. In fact, reliable evidence shows that one in four chronic pain patients prescribed opioids will develop an opioid misuse problem, and one in ten will become addicted to opioids. Further, these risks were known before Defendants began the aggressive marketing campaign. As to the assertion that behaviors indicating addiction are “not common in patients without a previous history of addiction,” Edlund *et al.*’s 2014 study shows that the largest contributor to risk of addiction is dose and duration (OR = 122 for opioid doses over 120 MMEs for 3 months or longer), a far more impactful risk than personal history of addiction (OR



3-9). (Edlund MJ, *et al.* The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. *Clin J Pain.* 2014;30:557-564 at p. 557.) It is false to equate feeling “euphoria” from opioids as a marker of addiction. Many people who get addicted to opioids do not endorse feeling euphoric from opioids. Indeed, many describe pain relief as the initial driver. Further, once people become addicted to opioids, they stop feeling euphoric effects. Instead they’re compelled to continue consuming opioids just to feel normal and avoid the pain of withdrawal.

- “The most common side effects of opioids include constipation, nausea and vomiting, sedation (sleepiness), mental clouding and itching. Some people may also experience dizziness or difficulty urinating. Respiratory depression, a decreased rate and depth of breathing, is a serious side effect associated with overdose. The good news is that most side effects go away after a few days.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0517)

**Comment:** In this patient-facing educational material, the risk of addiction is underplayed, not mentioned once in the section subheading “Most Common Side Effects.” Yet according to World Health Organization classification of risk, the risk of addiction to prescription opioids is “common” to “very common”: one in four persons prescribed an opioid for chronic pain will develop an opioid misuse problem, and at least one in ten will become addicted. (World Health Organization, CIOMS, [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/trainingcourses/definitions.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf), at p. 10.)

- “Usually has a friend who was addicted to fentanyl in med. school, failed out and is an addict? It’s amazing how often it happens??” Actiq Physician Segmentation Guide (TEVA\_MDL\_A\_01327080 at -7082)

**Comment:** This was from a sales training document to train sales specialists how to approach doctors who are more “cautious” in their opioid prescribing habits. The casual disregard for a personal exposure to addiction is consistent with a corporate culture in which every indication of the serious risks of addiction is framed as a sales obstacle to be overcome with marketing tactics. Further, this statement reveals that corporate executives fully understand the high prevalence of addiction to fentanyl products: “amazing how often it happens??”

## 2. Myth: The problem is the “addicts,” not the drug

- “Others are concerned that the average person will become addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem

is the increase in abuse of prescription drugs in the U.S. Persons with addictive disease (in the past, the term ‘addicts’ was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them ‘on the street’ for profit.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0515)

**Comment:** By implying that the “average person” need not fear addiction to prescribed opioids, and that the U.S. opioid crisis is the result of “Persons with addictive disease” who “obtained and misused these drugs,” the authors are suggesting that the addiction exists before the individual is prescribed opioids, excluding the possibility that a patient could become addicted through a prescription. With this misleading messaging, authors are perpetuating the myth that “legitimate” pain patients prescribed an opioid from a doctor can’t get addicted. In fact, as referenced in my Report, the CDC and the Director of NIDA the Report, Nora Volkow, have stated that anyone can become addicted to prescription opioids, and sources such as the ASPPH confirm that the opioid epidemic was fueled by the oversupply of prescription opioids. This misleading messaging further promotes the idea that by separating opioid-addicted persons as a distinct population, the remaining patients can be prescribed opioids without risk. The reality is that legitimate pain patients can and do get addicted through an opioid prescription.

- “Opioids get into the hands of drug dealers and persons with an addictive disease as a result of pharmacy theft, forged prescriptions, Internet sales, and even from other people with pain. It is a problem in our society that needs to be addressed through many different approaches.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0518)

**Comment:** Although it is true that diversion of prescription drugs is an important factor in this opioid epidemic, it is also true that people misuse, overuse, get addicted to, and die from prescription opioids received directly from their doctor to treat a medical condition. This statement is misleading because it implies that only people engaging in illegal activity are at risk. In fact, anyone exposed to an opioid for any reason is at risk.

### **3. Myth: No dose is too high; optimal dose is determined by titrating upwards until analgesia**

- “The other opioids can relieve severe pain. Their doses can be gradually increased over time. There is no ceiling dose as there is with the NSAIDs. As pain worsens, these medications continue to be useful unless side effects occur. It is a myth that opioids, like morphine should only be used

at the final stages of a seriously painful disease. When pain is severe, opioids should be considered.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0515)

**Comment:** Statements like these are misleading because they ignore that risks of opioids increase with increasing dose, and that many organs are adversely affected by opioids, not least of all the brain. Increasing doses can lead to the risks of tolerance, dependence, withdrawal, addiction, depression, cognitive impairment, and numerous other adverse effects, including risk of overdose and death.

#### **4. Myth: Dependence is normal, not a significant problem, and easily reversible.**

- “Physical dependence means that a person will develop symptoms and signs of withdrawal (*e.g.*, sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) if the drug is suddenly stopped or the dose is lowered too quickly. Physical dependence is normal; any patient who is taking an opioid on a regular basis for a few days should be assumed to be physically dependent. This does NOT mean you are addicted. In fact, many non-addictive drugs can produce physical dependence. To prevent withdrawal from occurring, the dose of the medication must be decreased slowly.” American Pain Foundation Guide for People Living with Pain (TEVA\_MDL\_A\_01090496 at -0517)

**Comment:** Comparing dependence on opioids to dependence on non-addictive drugs is a false analogy because opioids work on the brain’s reward pathway and are therefore reinforcing beyond their pain-relieving properties. Further, there is significant overlap between those who become dependent on opioids and those who become addicted to opioids, and this statement minimizes that significant overlap.

- “Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed. Because caregivers play an integral role in therapeutic success, it may be helpful for health care providers to educate both patients and their caregivers about pain management programs in a joint discussion. [Willis, 2007, 261-

262; AACPI, 2004, 6-7]” Fentora Introduction to Pain  
(TEVA\_MDL\_A\_00890305 at -0346)

**Comment:** Dependence and tolerance are serious physical conditions in themselves and are not, as the authors state, always “easily overcome through scheduled dosing decreases.” See Weimer *et al* regarding the great difficulty many opioid-dependent patients have with tapering opioids. (Weimer MB, *et al.* A chronic opioid therapy dose reduction policy in primary care, *Substance Abuse*, 2016;37:1,141-147)

#### 5. Myth: Pseudo-addiction – respond with more opioids

- “Certain behaviors are sometimes mistaken for addiction. If patients receive inadequate pain relief, they may exhibit drug-seeking behaviors. This is called pseudoaddiction. When these patients receive adequate pain management, they no longer exhibit the same behaviors. Patients in pain do not usually become addicted to opioids. [Kahan, 2006, 1082-1083; NPC and JCAHO, 2001, 17]” Fentora Introduction to Pain  
(TEVA\_MDL\_A\_00890305 at -0355)

**Comment:** As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue. A review article found that there was no empirical evidence to support such a diagnosis, and that impartial scientists have criticized its usage, whereas authors affiliated with the opioid sellers have advocated the concept. (Greene MS, Chambers RA. Pseudoaddiction: Fact or Fiction? An Investigation of the Medical Literature. *Curr Addict Rep* 2015;310-317. doi:10.1007/s40429-015-0074-7.)

**Appendix I.C: Janssen****Janssen Misleading Messaging****A. Benefits of Opioids Not Supported by Reliable Scientific Evidence****1. Myth: Opioids are effective for chronic pain**

- “Effective Pain Relief Improves Physical Function In Patients With Chronic Pain. Patients with chronic low back pain receiving opioid analgesia reported significantly greater reduction in pain intensity and improved exercise performance vs patients receiving placebo.” Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759- JAN-MS-00068828 at 8798

**Comment:** This quote is misleading because it is part of a “Chronic Pain Message Platform,” but it relies on short-term studies to support claims of long-term pain relief. There are not now and have never been any reliable scientific studies showing efficacy of opioids for chronic pain.

**2. Myth: Opioids are first-line treatment**

- “Duragesic: A First-Line Choice for Chronic Around-the-Clock Opioid Therapy. Consider as first-line for patients with moderate-to-severe chronic pain who require continuous opioid analgesia: Degenerative joint disease; Chronic back pain; Cancer pain; Has been shown to be effective in certain cases of chronic neuropathic pain.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at \*19 (produced natively).

**Comment:** By not distinguishing between cancer pain and non-malignant pain, or between acute and chronic pain, the statement is misleading, in that there was no reliable evidence that opioid therapy was effective for chronic, non-malignant pain. A similarly misleading statement appears in the 2007 DURAGESIC Patient Brochure for pain expected to last for “weeks or longer,” stating that DURAGESIC has been used “for more than 16 years to effectively relieve pain,” yet citing, as support for that claim, a 1995 article written by an industry employee that states, “Clinical trials have established the efficacy and safety of transdermal fentanyl for the treatment of cancer pain. Transdermal fentanyl is not licensed for the treatment of acute pain, *e.g.* postoperative pain, and should not be prescribed for this purpose.” JAN00222296\_POT-01DR1050AR2.pdf, at pp. 7, 28; citing Southam, “Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy,” *Anticancer Drugs* 1995; 6:29-34, at 29.

### 3. ***Myth: Opioids improve function and quality of life***

- "...we have enhanced our current promotional message to maximize our product benefits and address relevant issues among chronic pain physicians...research shows: 1) functionality is a key driver of brand selection, 2) functionality is the end-benefit of physician treatment goals and 3) no brand owns functionality." Duragesic Market Update, July 3, 2002. JAN-MS-00310227 at 0228.
- Janssen's *Let's Talk Pain* website states that the use of opioids for the treatment of chronic pain can lead to patients regaining functionality and features an interview claiming that opioids were what allowed a patient to "continue to function." *Resources for Pain Management: Understanding Tolerance, Physical Dependence and Addiction*, Let's Talk Pain, [https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real\\_story/addictions.html](https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real_story/addictions.html).
- Janssen's patient education guide *Finding Relief* states that opioids can make it possible for people with chronic pain to "return to normal, e.g., to get back to work, walk or run, play sports, and participate in other activities." JAN-MS-00829901 at JAN-MS-00829910.
- A consumer webcast video for Ultram ER contained the statement "Because my chronic pain was waking me up throughout the night, I worked with my doctors and found a medication called Ultram ER, that provides management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time. Ultram ER not only helped to manage my chronic pain, but because Ultram ER is a 24-hour treatment, I no longer found myself waking up due to chronic pain. This was and is important to my overall chronic pain management program, because sleep is a critical factor in my overall mood, which affects my relationships." ENDO-OPIOID\_MDL-03850803 at 0806.

**Comment:** The FDA reprimanded Janssen for its "quality of life claims, including but not limited to, 'And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE,' and '...without pain, patient's sleep better, increase daily activities, and spend more quality time with their families.' Health related quality of life claims such as these require substantial supporting evidence in the form of adequate and well-controlled studies designed to specifically assess these outcomes. Therefore, without substantiation from adequate studies, the claims presented in this 'homemade' promotional piece are misleading." FDA Letter to Janssen RE: NDA 19-813, March 30, 2000. JAN-MS-00238338 at JAN-MS-00238341, *see also* at JAN-MS-00238344- JAN-MS-



00238345. There was a further FDA reprimand for the webcast video because it “misleadingly implies that patients treated with the drug will experience an improvement in their sleep quality. The webcast cites no support of these claims and there is neither evidence nor substantial clinical experience to support this effect of Ultram ER. FDA Warning Letter. RE: NDA 21-692, ENDO-OPIOID\_MDL-03850803. There is no reliable evidence to date that opioid pain medications improve long-term function or quality of life.

## B. Risks Understated

### 1. *Myth: Addiction/abuse is rare/low/uncommon/less than 1%*

- “In 10 years of use, low and stable reported rate of abuse.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at \*17 (produced natively).
- “Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare. The Boston Collaborative Drug Surveillance Program study revealed only four cases of iatrogenic addiction among 11,882 patients without a prior history of substance abuse who received opioids for a broad range of indications.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at \*25 (produced natively).
- “[P]atients may have concerns: ‘I’m afraid I’ll become a drug addict.’ Addiction is relatively rare when patients take opioids appropriately.” Duragesic Website Pages, April 10, 2006. JAN00222151, at \*89 (produced natively).
- “Problematic Opioid Analgesic-Related Behavior Reported In An Evidence-Based Review Was Low. Structured evidence-based review on abuse/addiction and aberrant drug-related behaviors (ADRBs) in patients with chronic pain receiving chronic opioid analgesia. Abuse/addiction rate of 3.27% (24 studies, N = 2,507). Amongst patients with no previous or current history of abuse/addiction, the rate was 0.19%. ADRB rate was 11.5% (17 studies, N = 2,466). Among patients with no previous or current history of abuse/addiction, the rate was 0.59%.” Chronic Pain Management Message Platform, August 20, 2009. JAN-MS-00068759-JAN-MS-00068828 at 8811, citing Fishbain *et al.* Pain Med. 2008; 9:444.
- “[S]tudies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at \*2 (produced natively), referencing Definitions Related to the Use of Opioids for the Treatment of Pain: A Consensus Document from the

American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.

- “Given the relatively decreased potential of misuse of long-acting (*e.g.*, methadone) and sustained-release opioids (*e.g.*, transdermal fentanyl) in chronic pain patients, these may be preferred over short-acting opioids.” Speakers Notes, Assessing Risk of Substance Abuse, 2002. JAN-MS-00310473 at \*18 (produced natively).
- Speaker’s notes from a Janssen sales training presentation cite to Joranson (2000) to state that “investigators concluded that the trend of increasing medical use of opioid analgesics to treat pain does not appear to contribute to increases in the health consequences of opioid use.” JAN-MS-00302787, at \*29 (produced natively).
- Janssen’s *Prescribe Responsibly* website states that concerns about opioid addiction are “often overestimated,” and that “true addiction occurs in only a small percentage of patients.” Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.
- Janssen’s *Prescribe Responsibly* website states: “In those cases when a patient expresses concern about addiction,” it is important to have a further discussion, because if the concern turns out to fall within the technical definition of “physical dependence,” the patient’s addiction concerns can be overcome by “reassurance from the healthcare professional.” Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.
- Janssen’s patient education guide *Finding Relief* dismisses as “myths” the facts that opioids are addictive, can make functioning more difficult, and often must be prescribed in higher doses over time. JAN-MS-00829901, at JAN-MS-00829910.
- Janssen’s *Prescribe Responsibly* website states that addiction risk screening tools allow HCPs to identify patients predisposed to addiction, thereby allowing prescribers to manage the risk of opioid addiction in their patient populations. *Risk Assessment Resources*, <http://web.archive.org/web/201901292017000/http://www.prescriberesponsibly.com/risk-assessment-resources>.

- Janssen regarded the *Let's Talk Pain* and *Prescribe Responsibly* websites as integral to the launch of Nucynta ER. JAN-MS-00015864 at JAN-MS-00015878.
- Presentation for a Janssen unbranded campaign promoted as one of the “Key messages”: “Although many physicians are reluctant to prescribe controlled substances, the risks (for both patient addiction/misuse, and physician disciplinary action) are much smaller than commonly believed.” JAN-TX-00002318 at slide 13. The presentation also provided this “Execution tip”: “Avoid the Addiction Ditch...Use Portenoy’s study to create dialogue about Opiophobia as a barrier...Many HCP’s will find the 2.6% incidence of addiction to be extremely low.” JAN-TX-00002318 at slide 14.
- A Janssen sales training document proposed sample language to use on calls to prescribers, “it is a common misconception that the incidence of addiction and misuse is high when patients are prescribed an opioid. The reality is, according to Dr. Portenoy’s landmark registry study, behavior suggestive of misuse was seen in only 2.6% of patients. In addition, many physicians fear that if they prescribe opioids for too many of their patients, they might be subject to disciplinary action by their state medical boards. The reality is that only a tiny percentage of disciplinary actions have anything at all to do with controlled substances, and none of them were solely concerned with overprescribing.” JAN-MS-01135846 at 5852.

**Comment:** As detailed in the Report, addiction is common among patients treated with opioids (10-30% of patients treated with opioid pain medication will develop an opioid use disorder/addiction), and the risk of addiction increases with increasing dose and duration. Studies quoting low rates of addiction were methodologically flawed and biased by drug company sponsorship. The Porter and Jick letter was not relevant to addiction resulting from chronic opioid therapy. The Fishbain reference did not disclose that Fishbain was an expert witness for an opioid seller (Purdue); did not disclose that Fishbain had written an earlier review that reported addiction rates as high as 18.9%; and did not disclose the numerous flaws in the Fishbain 2008 article described in the Report. The reference to Joranson did not disclose that Joranson was also a paid consultant to Purdue and did not disclose that by 2004 even Joranson had published an updated report documenting substantially increased Emergency Department admissions for the period 1997-2002, compared to the period 1990-1996 covered by his previous article. (“In 2002, opioid analgesics accounted for 9.85% of all drug abuse, up from 5.75% in 1997.” Gilson, Ryan, Joranson and Dahl, *J Pain Symptom Manage*. 2004 Aug; 28(2):176-88.). Portenoy, assessing Oxycontin misuse/addiction, used a questionable denominator with 133 patients dropping out, excluded

patients with self-reported past or present substance or alcohol abuse, and was sponsored by Purdue. Portenoy, *et al.*, Long Term Use of Controlled-release Oxycodone for Noncancer Pain: Results of a 3-year Registry Study. *Clin. J. Pain* 2007; 23: 287-299, DOI: 10.1097/01.brs.0000186860.23078.a8.

## 2. *Myth: No dose is too high*

- Emails to district sales managers pushed higher dosage messaging for Ultram ER: “Focused message geared toward 200[mg]- get out of the ‘letter of the law’ mentality (ie-stop the state w/ 100[mg] for opioid naïve patients and just say other Dr.’s are having success starting at 200mg)” JAN-TX-00053505.
- Emails to sales representative and managers pushed a high dosage message: “We also discussed the importance of sampling- save the titration packs for the primary care physicians and the 200mg bottles for the specialists. Our goal is to get the patient to start on 200 mg or more if they need to titrate up. ‘Doctor, why would you start a patient on a minimal dosage of tramadol when your patient is in pain. The minimum dose of tramadol IR would be 200-400kmg daily...So, you need to start the patient on 200mg.’ The beauty of Ultram ER is the flexibility in dosing. We cannot flinch on the sale for fear of side effects.” JAN-TX-00277835 at 77836.
- “Doctor, there is no established ceiling dose for Nucynta ER” and “Note to Sales Representatives: A ceiling dose is the threshold at which additional dose increases produce no change in efficacy and often lead to greater side effects. It is a plateau effect that is common to most medications. However, it is important to note that pure opioid agonists, such as morphine, do not have a ceiling dose.” Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6379.
- “In your practice you may titrate your patients at your discretion, based on your assessment of their pain management needs.” Nucynta ER Frequently Asked Questions, November 17, 2011. JAN-MS-00016372-JAN-MS-00016397 at 6380. “There is no ceiling dose for opioids. Titrate the dose upward to obtain maximum pain relief without unacceptable side effects. Always prescribe rescue medication for breakthrough pain.” Optimizing Chronic Pain Management with Duragesic, December 14, 2001. JAN-MS-00653403, at \*26 (produced natively).

**Comment:** The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous

adverse effects, including death. The statement, “We cannot flinch on the sale for fear of side effects,” in the context of upselling higher doses, gives rise to particular concern, since it shows awareness of the accompanying increased risk, yet nevertheless promotes the higher dose.

**3. *Myth: Dependence is not a significant problem and is easily reversible***

- “Opioids can be discontinued in dependent patients without withdrawal difficulties by simply tapering them over about a week.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at \*24 (produced natively).
- “Physical dependence may be managed by gradually reducing the dose of the medication if the patient’s physician decides it is appropriate to discontinue therapy.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at \*1 (produced natively), (citing Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients: part 1: prevalence and diagnosis. *Oncology*. 1998; 4:517-521).

**Comment:** Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. “Tapering them over about a week” would cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

**4. *Myth: Tolerance – respond with higher dose***

- “Tolerance does not mean that the medication has lost its effectiveness. Rather, the dose must be adjusted to achieve an effective level of pain relief.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at \*2 (produced natively).
- “Increases in opioid doses may be required over the first few days or weeks of therapy during titration to response. Tolerance to opioid analgesia typically does not occur once an effective dose of opioid is identified and administered regularly.” Opioidphobia PowerPoint, August 1, 2001. JAN-MS-00653426, at \*26 (produced natively).
- “Tolerance rarely ‘drives’ dose escalation. Tolerance does not cause addiction.” Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at \*8 (produced natively).

**Comment:** These statements are misleading, because tolerance is common, is associated with addiction, and is in fact one of the DSM-5 criteria for addiction.

**5. Myth: Pseudo-addiction – respond with more opioids**

- “Pseudoaddiction is a term used to describe patient behavior that can occur when pain is under-treated. Patients with unrelieved pain may become focused on obtaining medications and may seem to inappropriately seek drugs.” Duragesic Information on Opioid Dependence, Tolerance and Addiction, 2002. JAN-MS-00303825, at \*2 (produced natively), (citing Savage S, *et al.*)
- “Pseudoaddictive behaviors mimic those of true addiction, but in reality may reflect undertreatment. This may include drug-seeking behavior, taking larger than prescribed doses, and running out of medications prematurely, tolerance, and withdrawal. Although adequate pain relief should eliminate the abnormal behavior if it is truly pseudoaddictive, it is important to recognize that pseudoaddiction and addiction can coexist.” Speaker’s Notes, Assessing the Risk For Substance Abuse, 2002. JAN-MS-00310473, at \*1 (produced natively) (citing Passik *et al.* 2000, p 73; Portenoy *et al.* 1997, p. 563.)
- “Pseudoaddiction: Syndrome of abnormal behavior resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of the clinical intention.” Addressing the Barriers to Effective Pain Management and Issues of Opioid Misuse and Abuse, 2013. JAN-MS-01509021, at \*19 (produced natively).
- Janssen’s *Let’s Talk Pain* website describes the concept of “pseudoaddiction” as “patient behaviors that may occur when pain is under-treated” but differs “from true addiction because such behaviors can be resolved with effective pain management.” *Resources for Pain Management: Understanding Tolerance, Physical Dependence and Addiction*, Let’s Talk Pain, [https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real\\_story/addictions.html](https://web.archive.org/web/20120322234928/http://www.letstalkpain.org/real_story/addictions.html).
- Janssen’s *Prescribe Responsibly* website states that addiction might be “pseudoaddiction,” defined as “a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed,” and “[t]ypically when the pain is treated appropriately, the inappropriate behavior ceases.” Keith Candiotti, M.D., *Use of Opioid Analgesics in Pain Management, Prescribe Responsibly*, <http://www.prescriberesponsibly.com/articles/opioid-pain-management>.



*Lembke Report*

*Confidential — Subject to Protective Order*

**Comment:** As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept. Further, by introducing the concept of pseudo-addiction, Defendants made it more difficult for prescribers to detect and treat prescription opioid addiction, encouraged prescribers to increase opioid doses, and thereby further endangered those patients who became addicted to the opioids received through the health care system.

**Appendix I.D: Endo Pharmaceuticals****Endo Misleading Messaging****A. Benefits of Opioids Not Supported by Reliable Scientific Evidence****1. Myth: Opioids are effective for chronic pain**

- “[P]ain leaders recognize the need... to arrive at a unified agenda and establish a framework that supports better understanding of this therapy and the benefits and risks of prescribing opioid medication. While the pain community must call attention to the epidemic of *chronic pain*, its undertreatment, and the *utility of opioid therapy as a safe and effective* strategy to relieve pain and improve functioning in appropriately selected and monitored patients, it also must acknowledge the societal and public health concerns raised by reports of increasing prescription drug abuse.” “Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management - A Roundtable Discussion,” American Pain Foundation. Published April 2008. (emphasis added). The Report states that it was “supported by an educational grant from Endo Pharmaceuticals.” ENDO-OPIOID\_MDL-02212377 at -2380-2381.
- “Pain affects more Americans than diabetes, heart disease and cancer combined. Now is the time to build consensus on pain management *on opioid use* in America and drive perceptions towards a more balanced view. Alleviating pain in patients with legitimate medical needs remains an important medical imperative. Patients deserve optimal pain relief, which includes access to *safe and effective* pain medications balanced with appropriate risk management. When properly prescribed by a healthcare professional and taken as directed, these medications provide *important pain relief and can improve functioning*.” *Id.* at -2381(emphasis added).
- “A key challenge is the *lack of scientific studies that have evaluated long-term safety and efficacy* of opioids for non-cancer pain.” *Id.* at 2380 (emphasis added).
- “The *absence of controlled clinical trials evidence must not be misinterpreted to be ‘lack of evidence.’* As defined by the principles of evidence-based medicine, the cumulative experience of myriad practitioners and their patients presents a robust body of evidence; however, the need for better science in this area is abundantly clear.” *Id.* at 2387 (emphasis added).

- “NEW OPTIONS TO HELP PHYSICIANS...STAY ON TOP OF LOW BACK PAIN SAFE AND EFFECTIVE FOR PATIENTS NOT RESPONDING TO STANDARD FIRST-LINE THERAPY.” Percocet brochure published April 2002. ENDO-OPIOID\_MDL-04929187 at - 9192.

**Comment:** These quotes exemplify the Industry’s misleading promotional messages, which perpetuated the unsupported claim that opioids are ‘safe and effective’ for ‘chronic pain,’ and minimized the importance of controlled trials showing safety and efficacy beyond 16 weeks. As to the claim of efficacy of opioids for chronic pain, there was not then, and there has never been, reliable evidence to support the claim. The Endo-sponsored report tries to have it both ways. While acknowledging the lack of “scientific studies that have evaluated long-term safety and efficacy,” the Report asserts that “cumulative experience” constitutes “robust evidence” under principles of evidence-based medicine. That is not correct. “Cumulative experience” is anecdotal and does not qualify as evidence-based medicine. While experience may *complement* scientific studies, experience is not a *substitute* for such studies, especially in the face of mounting evidence of harms. Further, a gold standard one-year randomized clinical trial (Krebs, 2018) demonstrated that opioids are not superior to non-opioid therapy for patients with chronic pain. This result refutes 20 years of the Industry’s reliance on anecdotal, non-scientific studies to claim that long-term opioid therapy is “safe and effective.”

**Comment:** The American Pain Foundation (APF), which published the 2008 Report, dissolved in 2012 due to irreparable economic circumstances after a ProPublica/Washington Post article “detailed its close ties to drugmakers.” The article found that APF’s “guides for patients, journalists and policymakers had played down the risks associated with opioid painkillers while exaggerating the benefits.” See Charles Ornstein, *et al.*, *American Pain Foundation Shuts Down as Senators Launch Investigation of Prescription Narcotics*, ProPublica (May 8, 2012) <https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups>.

## 2. Myth: Opioids are effective for long-term use based on short-term studies

- “Opana ER’s 12 hour dosing has been proven in many patient types including opioid-naïve patients with low back pain. In a clinical trial with opioid-naïve patients, 81% of patients on OPANA ER had a  $\geq 30\%$  pain score reduction compared with only 52% of patients on placebo. Even more impressive, greater than 70% of these patients achieved a  $\geq 50\%$  pain score reduction.” Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI\_LIT-00210473 at - 0475.

**Comment:** This quote, created for its sales representatives, was a reference to an article by Katz *et al.* which was biased and misleading, and included Endo employees as authors and was Endo sponsored. The claim that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief was misleading because the “>70%” figure, who purportedly achieved > 50% pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open label “enriched enrollment” phase which exposed all 325 to Opana. 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, *let alone* achieve >50% pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that “over 70%” achieved over 50% pain relief. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks. (ENDO-CHI\_LIT-00210473 at -0474) Also note that the Hale study, to be used for the same sales calls, explicitly stated in the abstract that Opana provides “long-term analgesia,” despite a study length of only 12 weeks. The claim of “long-term analgesia” is misleading in the context of a 12-week study. *See: Hale ME, et al. Efficacy and safety of OPANA ER (Oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. The Journal of Pain. 2007;8(2):175-184, at p. 175.*

### 3. Myth: Opioids are first-line treatment

- Listed under benefits of Opana ER - “Proven first line therapy for opioid-naïve patients.” Endo OPANA ER Call Plan Document Message and Support Materials, February 2007. ENDO-CHI\_LIT-00210473 at -0475.

**Comment:** By not distinguishing between acute pain and chronic pain, this quote sends the misleading message that using Opana ER for chronic pain is evidence-based. While there is reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there is no reliable evidence of efficacy for chronic, non-cancer pain.

**B. Risks Understated****1. Myth: Opioid therapy is “safe”**

- Comment: As to the assertion in the 2008 APF Report that opioid therapy is “safe” in “appropriately selected and monitored patients,” (*see above*): There were numerous studies that had reported a range of addiction as high as 24% before the opioid sellers began increased, widespread sale and distribution of opioids, without any reference to those data, and numerous additional, subsequent studies consistent with the earlier results. There was no reliable basis to assert that addictive drugs were not addictive simply because they had been prescribed by a doctor. As noted in the Volkow/McClellan article cited in the Report, “no patient is immune from addiction.” Regarding “appropriately selected and monitored patients,” as detailed in the Report, we do not have any reliable tools or screening instruments to predict who will get addicted to opioids prescribed in the course of medical treatment.

**2. Myth: Opioid dependence is not a significant problem and no different from other drugs**

- “Physical dependence and tolerance are related phenomena that occur with chronic use of many types of drugs, including many that are not associated with addiction or abuse (such as beta blockers for high blood pressure). Both result from changes in the body as it adapts to the constant presence of the drug. Physical dependence is due to adaptive changes that cause the body to depend on the drug’s actions to drive a process.” Oxymorphone Learning System, Module 3, Oxymorphone Risk Management Program (For Sales Training Background Purpose Only), 2006. ENDO-CHI\_LIT-00053284 at -3299.

**Comment:** This statement is misleading because withdrawal from “beta blockers for high blood pressure” cannot compare to withdrawal from opioids, which is so painful that it can lead to suicide, death due to autonomic instability, and pursuit of illicit sources of opioids.

**3. Myth: Pseudo-addiction – respond with more opioids**

- The Learning System manual noted that “[t]he physician can differentiate addiction from pseudoaddiction by speaking to the patient about his/her pain and increasing the patient’s opioid dose to increase pain relief.” *Id.* at -3299.

- “Pseudoaddictive behaviors such as clock watching (counting down the time until the next dose) will resolve when the pain is properly treated.” *Id.* at -3299.
- “The syndrome of drug-seeking behaviors that arises when a patient cannot obtain adequate relief with the prescribed dose of analgesic and seeks alternate sources or increased doses of analgesic is referred to as pseudoaddiction. This may be the result of increasing pain due to disease progression, development of a new condition, or inadequate instruction or dose provision by the clinician.” Opioid Analgesics for Pain Management: Critical Thinking to Balance Benefits & Risk [Endo had financial relationships with 5/5 faculty for this CME] June 2007, expires June 2009. CHI\_001222272 at -2279

**Comment:** As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at Purdue, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept. “Speaking to the patient” is particularly misleading advice, since numerous studies have documented the false statements provided by patients to their doctors in order to maintain access to addictive opioids.

#### 4. **Myth: Abuse Deterrent Formulations decrease risk of addiction**

- “Options . . . 1. The next generation of Opana ER was formulated using the INTAC™ technology which is designed to discourage misuse and abuse of the medication. 2. The next generation Opana ER was formulated to reduce the likelihood of abuse and misuse. 3. The FDA-approved formulation of Opana ER was developed with tamper-resistant properties to discourage abuse and misuse. 4. With a formulation that is designed to be crush-resistant, Opana ER represents the next generation of pain management medications. 5. The reformulated tablet is designed to make it more difficult for Opana ER to be split, chewed, crushed, or dissolved to release the medication more rapidly than intended.” Draft Communication Messages for Opana ER, November 17, 2011. END00099670 at -9670-9671.
- “A study of prescription opioid abusers in a drug rehabilitation program found that 80% tampered with opioid tablets to accelerate drug release by chewing or administering the drug intra-nasally or intravenously. The authors suggest that formulations that incorporate physical or pharmacologic impediments to altering the recommended routes of administration may deter tampering; The attractiveness of an opioid for



abuse is in large part dependent on characteristics of the tablet formulation particularly the ease with which it can be crushed or dissolved in fluids.”

Letter requesting support from Julie Suko Regarding: Reformulated Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, CII with INTAC® technology (Designed to be crush resistant), November 6, 2012. ENDO-OR-CID-00772464 at -2464.

**Comment:** Opana ER was at the center of the injection opioid epidemic in Scotts County, Indiana in 2015 that led to the spread of HIV in that community. “From November 18, 2014 to November 1, 2015, HIV infection was diagnosed in 181 case patients. Most of these patients (87.8%) reported having injected the extended-release formulation of the prescription opioid oxymorphone...Persons who reported injecting oxymorphone frequently described crushing, dissolving and cooking extended-release oxymorphone (Opana ER, Endo Pharmaceuticals).”<sup>1687</sup> In other words, “abuse via injection” was not more difficult. The most common way that people misuse and get addicted to prescription opioids, is to ingest oral formulations orally as prescribed. Although tamper-resistant formulations may make it more difficult to crush, snort, or inject these substances, that is no protection against getting addicted to them in the first place, taken as prescribed. Further, as with Opana ER, which was supposed to be tamper resistant, addicted persons were able to crush and inject it.

## 5. Myth: Addiction/abuse is rare/low

- “What is the risk of becoming addicted to a long-acting opioid?” “Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.” 2009 Opana ER “Instant Savings” card ad Resource Kit promising up to \$300 in savings. 2009 Opana ER “Instant Savings” card and Resource Kit, ENDO-CHI\_LIT-00541205 at -1211.
- “Most doctors who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.” Endo’s website for Opana, www.Opana.com (until at least 2012). END00474717 at -4739.

**Comment:** These comments are misleading because they suggest addiction is rare in patients treated with opioids. Addiction risk with opioid therapy is common, not rare.

<sup>1687</sup> See Peters, *et.al.*, “HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015” *N Engl J Med* 2016;375:229-39, at pp. 229 and 232.

**6. Myth: No dose is too high**

- “Some people taking opioids may need to take a higher dose after a period of time in order to have relief from their pain. This is ‘tolerance’ to opioids medications that doesn’t affect everyone who takes them and does **NOT** mean addiction. (Emphasis in original). If tolerance develops, it does not mean you will ‘run out’ of pain relief. Your healthcare provider can adjust your dose or prescribe another medicine.” 2009 Opana ER “Instant Savings” card and Resource Kit, ENDO-CHI\_LIT-00541205 at -1211.
- “[W]hat should I know about opioids and addiction?” “If tolerance does occur, it does not mean you will ‘run out of’ pain relief. Your dose can be adjusted or another medicine can be prescribed.” Understanding Your Pain: Taking Oral Opioid Analgesics brochure. ENDO-CHI\_LIT-00237187 at -7189.

**Comment:** In fact, tolerance is a good indicator that the patient will ‘run out’ of pain relief. Tolerance indicates neuroadaptation to the opioid molecule, and the need for higher doses to get to same effect and/or stave off withdrawal. Since higher doses are associated with more morbidity and mortality, increasing doses of opioids are dangerous. These statements perpetuate the misleading claim that tolerance is a benign condition that is not associated with addiction.

## Appendix I.E: Allergan

### Allergan Misleading Messaging

#### A. Benefits of Opioids Not Supported by Reliable Scientific Evidence

##### 1. Myth: Opioids are effective for chronic pain

- “Longer-acting agents are more effective than short-acting agents for chronic pain; “around-the-clock” dosing for “around-the-clock pain”. Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN\_MDL\_01741588 at -1596.

**Comment:** This quote exemplifies the claim that opioids are effective for chronic pain, which was not then, and has never been, supported by reliable evidence.

- “Morphine and morphine-like drugs work well for pain and are safe when taken as directed by a doctor.” *Id.* at -6826.

**Comment:** As detailed in the Report, there is not now and has never been reliable evidence that opioids are effective for long-term treatment of chronic pain.

##### 2. Myth: Opioids are first-line treatment

- “How does Kadian fit into your prescribing habits? If first line...Thank the HCP for their business and remind them of the key features and benefits of Kadian. If not first line: Why don’t you use Kadian first line?” Kadian Marketing Overview - Sales Representative Training, October 2011. ALLERGAN\_MDL\_00007268 at -7294. Same presentation used in February 2013, *see* ALLERGAN\_MDL\_00026506 at -6533.<sup>1688</sup>

**Comment:** The quote above does not distinguish between acute pain and chronic pain. The implied “key feature” of Kadian is its longer duration of action for “around the clock” pain, *i.e.* chronic pain. While there was reliable evidence of efficacy of opioids for acute pain, as noted above and in the Report, there was no reliable evidence of efficacy for chronic, non-cancer pain. It was misleading to make a blanket statement of efficacy without making this distinction clear.

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<sup>1688</sup> This text also appears in the Promotional Training Slides used to train Kadian sales representatives. *See* Exhibit 10 to the deposition of Mark Killion, Allergan\_MDL\_0026826 at -6828.

**3. Myth: Opioids are safer than the alternatives**

- “Maintenance therapy with opioids can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective NSAIDs, or acetaminophen . . .” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN\_MDL\_01741588 at -1598.

**Comment:** There was no reliable evidence to claim that opioids were “safer, or “perhaps” safer than NSAIDs or acetaminophen. As to NSAIDs, the best available evidence shows that opioids confer greater risk of mortality and adverse events. (*See* Solomon study in the Report ); also, the Krebs study (SPACE trial) in the Report, found more adverse events in the opioid group than among the non-opioid group that consisted of acetaminophen and NSAIDs, with a small percentage of patients on tramadol.

**4. Myth: Opioids improve function/quality of life**

- “Proven efficacy and improvement in quality-of-life (QOL) sleep scores in patients with chronic back pain.” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN\_MDL\_01741588 at -1632.
- “. . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated, pain can place stress on your body and your mental health” and “Chronic pain . . . can be inconvenient and can keep you from your daily tasks.” The FDA objected to these statements in prior brochures. Letter to FDA from Actavis, July 16, 2010. ALLERGAN\_MDL\_01237743 at -7750.

**Comment:** The above quotes imply that opioids will improve function and mental health, when the data show little or no improvement in function with opioid therapy, and more adverse medical events. Indeed the high drop outs rates in many opioid studies, even short term, suggest that many people do not tolerate opioids. Also, studies have linked the use of opioids with depression and suicidality, not improvements in mental health. Burgeoning evidence shows significant morbidity and mortality with opioids, increasing with dose and duration.

**B. Risks Understated****1. Myth: Addiction is rare**

- “Opioids can be used with minimal risk in chronic pain patients without a history of abuse or addiction.” Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. ALLERGAN\_MDL\_01741588 at -1596.
- “Clinicians who had been incorrectly trained to believe that taking opioids for a prolonged period would always result in addiction were surprised that most of these patients never exhibited any signs or symptoms of addictive disease.” California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0766

**Comment:** Opioids cannot be used for chronic pain without imposing significant risks of addiction, dependence, withdrawal and multiple adverse effects. It is misleading to claim that risks were “minimal.” Prior to the prescription opioid epidemic, clinicians were properly trained to understand that prescription opioids conferred significant risk of dependence, addiction and death. Clinicians were not trained to believe that addiction “always” occurred, and it is factually incorrect to imply otherwise.

**2. Myth: The problem is the ‘addicts,’ not the drug**

- “However, despite the continued unscientific beliefs of some clinicians, there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction. It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice.” Kadian Learning System. ALLERGAN\_MDL\_01052119 at 2254; *see also* California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0759

**Comment:** This quote perpetuates the misleading idea that the problem is the addicted patient, not the inherently addictive nature of the opioid. In fact persons with no personal or family history of addiction can become dependent on, addicted to, and die from opioids through a medical prescription.

**3. Myth: Tolerance - Respond with higher dose**

- “Upward titration of pure opioid agonists can theoretically be continued indefinitely, because there is no absolute ceiling effect to these medications. In practice, however, although this is sometimes performed

in cases of cancer pain, most physicians will try an alternative medication once they have exceeded their own comfort level with a given drug.” Kadian Learning System. ALLERGAN\_MDL\_01052119 at -2221.

- “Doses are titrated to pain relief, and so no ceiling can be given as to the recommended maximal dose especially in patients with chronic pain or malignancy. In such cases, the total dose of KADIAN should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions occur.” California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0845
- “Pseudotolerance – Pseudotolerance is the need for an increase in dosage that is not due to tolerance, but is due to other factors, such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior.” Kadian Learning System. ALLERGAN\_MDL\_01052119 at -2305.
- “It is important to recognize that tolerance and dependence (discussed above) do not indicate addiction. Rather, they are an expected consequence of taking opioids in moderate to high doses for a significant length of time. Proper use of opioids is not ‘maladaptive’ nor does it ‘interfere with the person’s life’; instead it allows the patient to return to a functional life.” California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0711

**Comment:** The statements above are misleading because they omit that increased dose increases risk of dependence, addiction, and numerous adverse effects, including death. “Pseudotolerance” is not a recognized diagnosis, whereas “tolerance” is almost universally the reason why opioid users seek increased dosage of the drugs.

#### 4. Myth: Pseudo-addiction – respond with more opioids

- “The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of “pseudoaddiction.” Pseudoaddiction is a set of behaviors . . . that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.” Kadian Learning System. ALLERGAN\_MDL\_01052119 at -2150.
- “Pseudoaddiction—Pseudoaddiction is drug-seeking behavior that seems similar to addiction but is due to unrelieved pain. This behavior stops once



the pain is relieved, often through an increase in opioid dose.” Kadian Learning System. ALLERGAN\_MDL\_01052119 at -2305.

- “Pseudoaddiction: Behaviors (that mimic addictive behaviors) exhibited by patients with inadequately treated pain.” California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0690

**Comment:** As detailed in the Report, pseudo-addiction is not a reliable diagnosis; the term pseudo-addiction was developed by a physician (Haddox) who became an executive at an opioid seller, and a review article found that impartial scientists criticize its usage, whereas authors affiliated with the opioid sellers advocate the concept.

## 5. Myth: Opioid dependence is easily reversible

- “Development of Tolerance and Physical Dependence is a major reason some clinicians feel opioid therapy should be limited for patients with CBP. Most clinicians do not consider this a major issue, however. Although tolerance and dependence do occur with long-term use of opioids, many studies have shown that tolerance is limited in most patients with CBP. Physical dependence simply requires a tapered withdrawal should the opioid medication no longer be needed.” Kadian Learning System (Altier Ex. 2 / ALLERGAN\_MDL\_01610522 at 0848); *see also*, California Killion deposition Exhibit 9, Kadian Learning System, Allergan\_MDL\_01450683 at -0758

**Comment:** Dependence and tolerance are serious physical conditions in themselves, leading to increased doses and addiction in a subset of patients, and to long, slow, and often failed attempts at tapering. Abrupt discontinuation or rapid tapering of opioids can cause extreme suffering in the majority of patients on chronic opioid therapy, and may even lead some to experience suicidal thoughts and/or turn to illicit sources of opioids.

## Anna Lembke, M.D. Report

# APPENDIX II

Summary of Documents from the University of Wisconsin  
Pain and Policy Study Group (PPSG)

**Appendix II: Documents from the University of Wisconsin Pain and Policy Study Group**

1. Documents produced by the University of Wisconsin Pain and Policy Studies Group (PPSG) in this case are supportive of Dr. Joel Saper's statements concerning the relationship between "narcopharma," as he referred to the Industry, and David Joranson, who was Director of the PPSG. (*See* Report at section §C.4.k.) These documents provide evidence that the Industry funded PPSG over a period of many years, and that PPSG, in turn, carried out programs that benefitted the Industry by increasing access to opioids and limiting regulatory scrutiny of prescribing doctors.
2. On September 9, 1996, John Stewart wrote an email to Robert Kaiko of Purdue Pharma, recounting a discussion with David Joranson and Sophie Colleau at a pain conference in Vancouver, and Dr. Colleau's follow-up letter that included a reference to a UN report concluding that "the medical need for opioids is far from being met, and recommend[ing] specific steps that should be taken by governments, non-governmental organizations and health professionals- to increase the availability and use of opioids." Stewart informs Kaiko that "In the past, we have provided modest financial support for the Wisconsin Pain Research Group (in the form of annual corporate membership) and would be inclined to provide same (\$1,000 to \$2,000) toward this activity." Kaiko wrote back "They are seeking support that will not only cover this, but also, subsequent issues of the publication. To date I believe they are planning for 5k from Janssen and from Purdue 4k (2k in basic support and 2k for ?# copies in Spanish for our use in Latin America.)" PPLPC013000017513.
3. On December 20, 1996, PPSG Director Joranson and several others wrote a letter to "Dear Colleague," to inform about "the new Pain & Policy Studies Group (PPSG)," following the departure of the former head of the Pain Research Group to a new position. The letter advised that, "In the US, our group will continue its work to identify and address regulatory barriers to pain management . . . . We will expand our work with cancer and palliative care organizations and governments in a number of countries in order to achieve more balanced opioid regulation and improved availability of opioid analgesics." PDD1701481531. The stated goals of PPSG thus included making opioids more available for treatment of pain, an objective that matched well to those of the sellers of such drugs.
4. On October 5, 2000, Director Joranson sent an email to David Haddox and Robert Kaiko of Purdue Pharma, enclosing four items that Joranson had been working on, including a document titled, "Evaluating federal and state policy for balance," which had also been sent to Dr. Sackler. Dr. Joranson's email closed with, "Hope to have a cocktail or something with you in not too long!" Haddox replied, "I think it is an excellent work product." WIS\_PPSG\_001791. As noted throughout the PPSG documents, the principle of "balance" asserts that efforts to control diversion and abuse should not interfere with access to prescription opioids for pain; this principle was central to the Pharmaceutical Opioid Industry's ability to achieve widespread opioid use.

5. On August 30, 2001, Joranson wrote to Chris Neumann, Senior Director of Medical Education at Purdue Pharma, to acknowledge receipt of a \$75,000 grant to “help us maintain our program and accomplish our pain and policy goals.” WIS\_PPSG\_013938.
6. On September 9, 2002, Joranson wrote to Robert Kaiko of Purdue, regarding “the points I would make about the value of our work: ... 2. “We have improved state medical board policies: ... Many states now have improved pain/opioid policies that address concerns about regulatory scrutiny; we developed much of it from behind the scenes, we wrote the two models that states have used, the medical board guidelines from CA and the model guidelines of the federation of state medical boards... 4. Evaluation of state policies for impediments to the use of opioids for pain.” WIS\_PPSG\_006938
7. On October 9, 2002, Joranson again wrote to Mr. Kaiko, expressing appreciation for support provided by Purdue “for the past several years. Without your support, some of the progress reported below would not have been possible.” Joranson then asked for an additional grant of \$175,000 for this year, renewable for two more years. WIS\_PPSG\_006457.
8. On February 21, 2005, PPSG Director Joranson/PPSG gave a presentation to the American Pain Society, entitled, “Pain Policy in the U.S.: Are We Moving Forward?” The presentation included slides providing results of 3 national surveys of medical board members, in 1991, 1997, and 2004, under the heading “Education and research with medical regulators.” The next slide stated that “Prescribing an opioid analgesic for more than several months to treat a patient with Chronic non-cancer pain was “Lawful/generally accepted medical practice for 12% (1991), 33% (1997) and 67% (2004) of surveyed medical boards.” WIS\_PPSG\_000703, produced natively at \*6. PPSG’s Industry-funded efforts to remove prescribing restrictions significantly contributed to this drastic change in the acceptability of opioid treatment of chronic non-cancer pain.
9. Joranson’s 2005 presentation continued with a description of PPSG’s Model Policy Development, in particular, the FSMB Model Guidelines (1998) and FSMB Model Policy (2004), adopted in full by 13 states and in part by 12 states. The Model Policy advanced by PPSG “Recognizes need for opioids;” “Pain relief part of quality medical practice;” “Should not fear investigation;” and that “Inappropriate tx [treatment] includes over, under, non-treatment, continued ineffective tx.” (*Id.* at \*8-\*10). The designation of “undertreatment” of pain as “inappropriate” was a common theme in the promotion of opioids as the solution. The question of undertreatment of pain and the scope of the population arguably affected vary widely according to how the terms are defined. Regardless, the use of long-term opioid therapy is not and has never been the solution to chronic non-cancer pain.
10. Joranson’ presentation included a slide on “The Principle of Balance,” which stated, “Central to protecting public health and safety: Opioids are safe and

effective, necessary,” and that “Opioids have potential for abuse, pose risks.” (*Id.* at \*16). Reliable scientific evidence demonstrates that opioids are dangerous and deadly, not “safe;” no reliable scientific evidence demonstrated that opioids were effective for the treatment of chronic non-cancer pain. Joranson’s industry-funded presentation was misleading.

11. Another of Joranson’s February 2005 presentation slides listed “16 States Improved Pain Policies (2000-2003). “Examples of Policy Changes” included “Encourage pain management, pain management part of quality professional practice, address fear of regulatory scrutiny.” (*Id.* at \*18-\*19). Eight slides are devoted to the topics of diversion and abuse (*Id.* at pp. \*23-\*30). The presentation stated, “The reasons for increased abuse should be studied, taking into consideration all the sources of abused opioids, including deliberate criminal activities to divert opioids from all levels of the distribution system. Source and amount matter. Meanwhile, we should ensure that efforts to address abuse and diversion do not interfere in pain management.” (*Id.* at \*31). No slides in the presentation are devoted to risk of addiction or the powerful addictive properties of prescription opioids, including the risk to individuals who are receiving opioids as medical treatment, and not only to “abusers.”
12. On June 6, 2005, PPSG Director David Joranson and Assistant Director Aaron Gilson wrote to Robert Kaiko, VP of Clinical Research at Purdue and Pamela Bennett, Purdue, Director of Advocacy, to express appreciation for “the last three years of financial support that Purdue Pharma has provided to [PPSG], amounting to \$100,000 annually for the US program and \$175,000 annually for the international program.” This amounts to \$825,000 of financial support to PPSG from Purdue alone, in that 3-year period. The letter summarized PPSG’s “recent achievements” and requested an additional \$2.2 million from Purdue for the years 2006-2010. The first listed “achievement was as follows: “In the USA, between 2000 and 2003, 16 States took legislative and regulatory actions to improve their pain policies. Many of these actions were based on our evaluations, recommendations and technical assistance and were accomplished in collaboration with many governmental and nongovernmental groups which use PPSG policy evaluations as a road map.” WIS\_PPSG\_008286.
13. In an August 2005 email thread referencing the enactment of the “North Dakota Pain Bill,” an email was sent to Aaron Gilson, Assistant Director of PPSG, asking: “Did you guys have a hand in this one? This is certainly what I’ve espoused for years, since we realized intractable pain acts weren’t really that helpful—that all we needed in statute was a statement that practitioners could legally prescribe opioids for pain.” WIS\_PPSG\_000026; WIS\_PPSG\_000036. Gilson responded, “I’m impressed that you could detect our finger prints . . . I’ll wear gloves next time. Yes, we worked with Bruce Levi, Executive Director of the North Dakota Medical Association, to change ND’s IPTA [Intractable Pain Treatment Act] to a general pain statute, which also removed the prescribing restriction for ‘addicts.’” WIS\_PPSG\_000026; WIS\_PPSG\_000036. This exchange is indicative of not only the type of PPSG projects that benefited the

Industry by easing prescribing restrictions and penalties, but also shows the surreptitious, behind-the-scenes nature of PPSG's efforts.

14. In a November 2005 "Prospectus," PPSG listed a number of policies and programs to attract financial support. The Prospectus described PPSG's promotion of "the principle of 'balance' which recognizes that policies aimed at preventing drug abuse must not interfere with medical practice and patient care." To promote that policy, PPSG published "State Profiles that identify provisions in each state that have the potential to enhance or impede pain management. ... PPSG assigns grades to each state to draw attention to the need to improve pain policy. ... A Progress Report Card compared the policies in 2003 with those in 2000 and found that many states had improved the degree of balance in their pain and regulatory policies. PPSG identifies and recommends 'best' or model policies and assists in their development." WIS\_PPSG\_008292 at pp. 2-3. The "Accomplishments" section of the Prospectus stated, "PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management, now entitled Model Policy for the Use of Controlled Substances for Pain Management." (*Id.* at p. 4). The FSMB Model Guidelines played a significant role in exacerbating the prescription opioid epidemic, by eliminating or reducing restrictions on use of opioids for pain, and by threatening regulatory action for "undertreated pain."
15. PPSG also worked with the FSMB to develop and present an educational program for "workshops for state medical board members held across the U.S.; PPSG staff served as faculty, and administered a pre- and post-test survey to evaluate changes in knowledge and attitudes as a result of workshop participation." WIS\_PPSG\_008292, 11/30/2005.
16. On December 1, 2005, Joranson and Gilson of PPSG wrote to Bobbie Sue Brown, Clinical Development & Education Manager-Southwest, at Endo Pharmaceuticals, recounting the work of PPSG and requesting \$225,000 for the period 2006-2008. WIS\_PPSG\_007994.
17. A document titled, "U.S. Program Accomplishments: July 2009-June 2010," stated: "PPSG remains a member of the Federation of State Medical Boards Research and Education Foundation's advisory committee that recently developed a handbook to educate physicians about the Federation's Model Policy to promote safe and effective prescribing and reduce the risk of abuse, addiction, and diversion of opioids and other controlled substances in office-based pain management; the Handbook was published mid-2007 and is being made available to state medical boards to distribute to their licensees. [Fishman SM. Responsible opioid prescribing: A physician's guide. Washington, DC: Waterford Life Sciences; 2007.]" WIS\_PPSG\_007680, 02/07/2011, at p. 3.
18. The 2007 Fishman Handbook encouraged use of prescription opioids for chronic pain, despite absence of reliable evidence of long-term efficacy. Dr. Fishman's disclosure for a Continuing Medical Education (CME) program based on the



Handbook listed Endo, Janssen and Cephalon among his financial supporters. [https://archive.org/stream/279187-responsible-opioid-prescribing-info/279187-responsible-opioid-prescribing-info\\_djvu.txt](https://archive.org/stream/279187-responsible-opioid-prescribing-info/279187-responsible-opioid-prescribing-info_djvu.txt). The CME website listed the consortium members who supported publication of the Handbook, including Purdue Pharma, Endo, Cephalon, Alpharma, and the PPSG; the CME target audience was described as “Physicians who prescribe opioid analgesics as part of pain management strategies in their clinical practice.” (*Id.*) In short, PPSG cooperated with the Pharmaceutical Opioids Industry to produce a Handbook funded by the Industry to promote its views of “responsible prescribing;” that book was then used to “educate” physicians for CME credit, to be earned by reading the book and passing an online test on its contents.

19. The “U.S. Program Accomplishments: July 2009-June 2010” document also included the following entry: “PPSG published a review article describing the implications of inaccurate addiction-related terminology, contained in current federal and state laws, regulations, and guidelines/policy statements, on effective pain management and patient care; data used to inform sections of this manuscript was obtained through a recently-completed grant to examine the legislative and regulatory origins of restrictive policy language that currently is present in state law and has a potential to interfere with the adequate and effective use of controlled substances for pain management. [Gilson AM. The concept of addiction in law and regulatory policy: A critical review. *Clinical Journal of Pain*. 2010; 26(1):70-77.]” WIS\_PPSG\_007680 (emphasis added). Removing restrictions and interference with opioid prescribing were the stated goals of PPSG and aligned with its Industry funders.
20. A PPSG Spreadsheet lists financial contributions from the Pharmaceutical Opioid Industry between November 2000 and August 2007, including: Purdue Pharma, \$1,256,500; Janssen/J & J: \$238,990; Endo, \$140,000; Ortho-McNeil, \$125,000; Cephalon, \$25,000; Alpharma, \$25,000; Roxane, \$15,000; and Abbott, \$15,000 for a total of \$1,840,490. The spreadsheet lists 27 separate contributions by Purdue, and 10 each by Janssen/J&J and Endo; the frequency and collegial nature of the communications between PPSG and company representatives like David Haddox suggests a cooperative relationship. Additional payments occurred outside of the years covered by the spreadsheet. WIS\_PPSG\_007783.
21. A presentation by Joranson on February 16, 2008 disclosed financial relationships with Abbott, Alpharma, Cephalon, Endo, Ortho-McNeil, and Purdue Pharma. WIS\_PPSG\_007991. However, Joranson’s presentation slides did not include such disclosures in February 2005. WIS\_PPSG\_000703.
22. A 2011 spreadsheet lists the following contributions as “Pending”: Actavis, “to be \$55k;” Allergan \$50,000; Endo, \$46,106; \$649,779; \$46,057; and \$75,000; Janssen Ortho Pricara, \$50,000; and \$10,000; and Purdue, \$50,000. WIS\_PPSG\_003892.

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23. These documents provide supportive evidence for my opinion that one of the ways that the Pharmaceutical Opioid Industry created the opioid epidemic in the United States was by funding the PPSG to “educate” the medical community as to the “necessity” for such drugs, to influence state legislatures to increase access while loosening restrictions on prescribing, and to change the very culture of opioid prescribing, by suggesting that failing to prescribe opioids was tantamount to “undertreating” pain and violating a patient’s “rights.”

## Anna Lembke, M.D. Report

# APPENDIX III

Case Specific Data: Cobb County, Georgia

**Appendix III: Case specific data and information:****A. Background of the Case**

1. It is my understanding that the Plaintiff in this action is Cobb County, Georgia.
2. It is my understanding that the remaining Pharmacy Defendants in this action are as follows: Kroger and Publix.

**B. Opioid Prescribing/Dispensing**

1. Opioid prescriptions in Cobb County increased from 74.9 prescriptions per 100 persons in 2006 to a peak of 78.6 in 2010.<sup>1689</sup> Not reflected in this data is the substantial increase in prescribing that occurred between the late 1990s and early 2010s in the US overall.<sup>1690</sup>

Year	Opioid Dispensing Rate Per 100 Persons (U.S.) <sup>1691</sup>	Opioid Dispensing Rate Per 100 Persons (Georgia) <sup>1692</sup>	Opioid Dispensing Rate Per 100 Persons (Cobb County) <sup>1693</sup>
2006	72.4	79.8	74.9
2007	75.9	82.5	75.7
2008	78.2	86.3	78.0
2009	79.5	88.2	78.5
2010	81.2	90.2	78.6
2011	80.9	88.6	75.3
2012	81.3	89.4	73.0
2013	78.1	86.6	68.7
2014	75.6	83.8	65.0
2015	70.6	79.4	61.4
2016	66.5	77.8	61.3
2017	59.0	71.3	54.6
2018	51.4	63.2	47.1
2019	46.8	51.8	44.5
2020	43.2	54	38.9

<sup>1689</sup> Centers for Disease Control and Prevention. U.S. County Opioid Dispensing Rates, 2006-2020.

<sup>1690</sup> See Report Section 3.

<sup>1691</sup> Centers for Disease Control and Prevention. U.S. Opioid Dispensing Rate Maps, 2006-2020; Centers for Disease Control and Prevention. United States Dispensing Rate Maps (2019-2022). Last reviewed: December 11, 2023. <https://www.cdc.gov/drugoverdose/rxrate-maps/index.html>.

<sup>1692</sup> Centers for Disease Control and Prevention. U.S. State Opioid Dispensing Rates, 2006-2020; Centers for Disease Control and Prevention. Opioid Dispensing Rate Maps: State Opioid Dispensing Rates (2019-2022). Last Reviewed: October 31, 2023. <https://www.cdc.gov/drugoverdose/rxrate-maps/opioid.html>.

<sup>1693</sup> Centers for Disease Control and Prevention. U.S. County Opioid Dispensing Rates, 2006-2020; Centers for Disease Control and Prevention. Opioid Dispensing Rate Maps: County Opioid Dispensing Rates (2019-2022). Last Reviewed: October 31, 2023. <https://www.cdc.gov/drugoverdose/rxrate-maps/opioid.html>.

Year	Opioid Dispensing Rate Per 100 Persons (U.S.) <sup>1691</sup>	Opioid Dispensing Rate Per 100 Persons (Georgia) <sup>1692</sup>	Opioid Dispensing Rate Per 100 Persons (Cobb County) <sup>1693</sup>
2021	42	52.8	35.4
2022	39.5	49.8	33.4

2. A 2018 study of Georgia Medicaid pharmacy claims from 2009 to 2014, concluded “that potentially inappropriate prescribing practices are common and are increasing over time in the Georgia Medicaid population across all demographic categories...”<sup>1694</sup> The study reported that the “percentage of Medicaid enrollees with at least 1 or more indicators<sup>1695</sup> of potential inappropriate prescriptions slightly increased from 17.17% to 18.21% during the study time frame” and the “incidence rate of potential inappropriate prescribing practices per patient increased more than 58% over the 6 years.”<sup>1696</sup> As detailed in my report, inappropriate prescribing of opioids is primarily due to false and misleading promotion to doctors, overstating the benefits and understating the risks.
3. Since July 2017, dispensers in Georgia have been required to enter prescription information for Schedule II-V controlled substances within 24 hours of dispensing.<sup>1697</sup> Prescribers were required to check the PDMP before prescribing schedule II opioids, cocaine derivatives, or benzodiazepines (with some exceptions) starting on July 1, 2018.<sup>1698</sup> According to the Georgia Prescription Drug Monitoring Program Report, “Georgia saw improvement in opioid prescribing practices from 2017 to 2018...”<sup>1699</sup> In Cobb County, the percent of patient days with overlapping opioid and benzodiazepine prescriptions went from 11.8% in 2016<sup>1700</sup> to 10.5% in 2018.<sup>1701</sup> As detailed in my report, defendant pharmacies could have and should have mandated checking the Georgia Prescription Drug Monitoring Program much earlier. This change reduced, but did not eliminate, the misuse and diversion of prescription opioids that contributed to the opioid epidemic.

<sup>1694</sup> Jayawardhana, J., Abraham, A. J., & Perri, M. (2018). Opioid Analgesics in Georgia Medicaid: Trends in Potential Inappropriate Prescribing Practices by Demographic Characteristics, 2009-2014. *Journal of managed care & specialty pharmacy*, 24(9), 886–894. <https://doi.org/10.18553/jmcp.2018.24.9.886>

<sup>1695</sup> The study measured potentially inappropriate prescribing practices using the following 5 indicators: (1) overlapping opioid prescriptions, defined as opioid prescriptions that overlap by 7 days or more; (2) overlapping opioid and benzodiazepine prescriptions, defined as opioid and benzodiazepine prescriptions that overlap by 7 days or more; (3) overlapping opioid and buprenorphine/naloxone prescriptions, defined as opioid and buprenorphine/naloxone prescriptions that overlap by 1 day or more; (4) LA/extended release opioids prescribed for acute pain; and (5) high daily doses of opioid prescriptions, defined as receiving more than 100 MMEs.

<sup>1696</sup> Jayawardhana, J., Abraham, A. J., & Perri, M. (2018). Opioid Analgesics in Georgia Medicaid: Trends in Potential Inappropriate Prescribing Practices by Demographic Characteristics, 2009-2014. *Journal of managed care & specialty pharmacy*, 24(9), 886–894. <https://doi.org/10.18553/jmcp.2018.24.9.886>

<sup>1697</sup> Georgia Department of Public Health. Prescription Drug Monitoring Program Report, Georgia, 2018, at p. 3.

<sup>1698</sup> *Id.*

<sup>1699</sup> *Id.*, at p. 4.

<sup>1700</sup> Prescription Drug Monitoring Program, Georgia, 2016-2017, County Level Data at p. 8.

<sup>1701</sup> Prescription Drug Monitoring Program, Georgia, 2018, County Level Data at p. 10.

4. From 2006 to 2019, Publix pharmacies in Cobb County, GA received 26,758,930 opioid pills.<sup>1702</sup> The Publix pharmacies just in Marietta received 9,444,880 pills of that total,<sup>1703</sup> or approximately 155 pills per person in Marietta.<sup>1704</sup> In the same period, Kroger pharmacies in Cobb County received 25,033,480 opioid pills.<sup>1705</sup> Just the two Kroger stores in Powder Springs, GA received 4,581,660 opioid pills,<sup>1706</sup> enough for 271 pills per resident.<sup>1707</sup>

### C. Prescription Opioid Overdose Deaths

1. An analysis of data from the National Vital Statistics system found rates of estimated prescription opioid overdose deaths in Cobb County to range from 7.94 per 100,000 in 2017 to 3.68 per 100,000 in 2019.<sup>1708</sup> In my opinion, the decrease between 2017 and 2019 is due at least in part to decreased opioid prescribing and other interventions to target the epidemic described above.
2. The Georgia Department of Public Health reported that in 2017, 43.5% of decedents in opioid-involved overdose deaths had an opioid prescription filled within 180 days of death.<sup>1709</sup> In comparison, 31.9% of decedents in non-opioid involved overdose deaths had an opioid prescription filled within 180 days of death.<sup>1710</sup>
3. “Relative to other states, Georgia ranks in the top 12 states for the number of prescription opioid overdose deaths in 2015. Between the years of 1999 and 2016, deaths due to prescription opioids increased more than tenfold in Georgia from 50 deaths in 1999 to 715 deaths in 2016.”<sup>1711</sup> In 2016 in Georgia, more than six out of 10 (65%) drug overdose deaths involved opioids.<sup>1712</sup>

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<sup>1702</sup> Washington Post, “Drilling into the DEA’s Pain Pill Database” (updated September 12, 2023). See Cobb County, GA pharmacy data. <https://gfx-data.news-engineering.aws.wapo.pub/ne-static/arcos/v2/summary/arcos-ga-cobb-13067-pharmacy.csv>

<sup>1703</sup> *Id.*

<sup>1704</sup> The population of Marietta, GA was 60,972 in 2020. U.S. Census Bureau. *QuickFacts Marietta City, GA*. <https://www.census.gov/quickfacts/fact/table/mariettacitygeorgia/POP010220#POP010220>

<sup>1705</sup> Washington Post, “Drilling into the DEA’s Pain Pill Database” (updated September 12, 2023). See Cobb County, GA pharmacy data. <https://gfx-data.news-engineering.aws.wapo.pub/ne-static/arcos/v2/summary/arcos-ga-cobb-13067-pharmacy.csv>

<sup>1706</sup> *Id.*

<sup>1707</sup> The population of Powder Springs, GA was 16,887 in 2020. U.S. Census Bureau. *QuickFacts Powder Springs city, GA*. <https://www.census.gov/quickfacts/fact/table/powderspringscitygeorgia/POP010220#POP010220>

<sup>1708</sup> Expert Report of Dr. Katherine Keyes, *Cobb County, v. Purdue Pharma, et al.* Case No. 1:18-op-45817-DAP, Schedule A – Case Track 8 – Cobb County, at p. 6.

<sup>1709</sup> Dinwiddie, A.T. *Drug Overdose Deaths in Georgia, SUDORS & NVDRS* [PowerPoint slides]. Georgia Department of Public Health. <https://dph.georgia.gov/document/document/opioid-overdoses/download>, at p.8.

<sup>1710</sup> *Id.*

<sup>1711</sup> Valentini CA, Jayawardhana J. Drug overdose deaths in Georgia: impact of rural versus non-rural counties. *Journal of Pharmaceutical Health Services Research*. 2019;10:341-346, at p. 342.

<sup>1712</sup> *Id.*, at p. 341.



**D. Georgia Pharmacists' Work Environment**

1. In 2020, the Georgia Pharmacy Association Board asked Georgia pharmacists to anonymously share their concerns regarding working conditions at pharmacies.<sup>1713</sup> The majority of respondents said that “corporate demands and protocols had been changed for the worse in the last decade [and] they were concerned the increase in workload could result in a mistake that could harm their patients.”<sup>1714</sup> While specific pharmacies were not mentioned, comments to the board described:
  - a. “I have been a pharmacist since 2003. I began my career with a (chain) pharmacy filling 2800-3000 prescriptions per week. Everything began to change around 2014-2015. Our performance evaluations began to be tied to pharmacy metrics which set unattainable goals. In 2017, our labor metric was reconfigured, and staffing was drastically cut; pharmacists hours reduced from 190 to 160 per week, eliminating any pharmacist overlap. We knew we would be punished if we had multiple errors. This led to many of us not reporting errors. My partners and I only reported errors when a patient actually ingested an incorrect medication or was angry. Most errors were corrected, and we apologized.”<sup>1715</sup>
  - b. “I have been a retail pharmacist since graduating in 2002 and have been in pharmacy since 1993. Yes, there have been many exciting changes to the profession that have advanced our practice. However over recent years, the profession of pharmacy is anything but professional.”<sup>1716</sup>
  - c. “At the end of a workday, a pharmacist should not have to be fearful if or how many misfills they had that day. We should be allowed to do our job; to take care of our patients and help them live healthier lives.”<sup>1717</sup>
  - d. “We are told to do ‘quality’ comprehensive medication reviews, yet we barely have time to go to the bathroom once in a 12 hour shift, let alone get a break to eat. Where is the time to accurately research issues or to have quality interactions with patients? It’s only a matter of time before mistakes are made. We only pray that it is a small mistake and not one that causes harm or takes a life.”<sup>1718</sup>
2. In 2021, Kroger conducted a “Pharmacy Associate Experience Survey”<sup>1719</sup> where pharmacy staff from Kroger’s Atlanta division expressed the following concerns:
  - a. “Pharmacy has transformed into drug seeker paradise.”<sup>1720</sup>

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<sup>1713</sup> Davidson, M. (2022, February-March). Toxic Work Environments. *Georgia Pharmacy*, 31.

<sup>1714</sup> *Id.*

<sup>1715</sup> *Id.*

<sup>1716</sup> *Id.*

<sup>1717</sup> *Id.*

<sup>1718</sup> *Id.*

<sup>1719</sup> Corporate deposition Kroger through Laura Raney, *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Tracks 9 and 10), August 29, 2023 (herein after “Raney Dep.”), at 75:5-83:11; Raney Dep. Exhibits 7 and 8.

<sup>1720</sup> Raney Dep. Exhibit 8 (at Row 1090)

- b. “we need to hire people, we are extremely short staffed and rph are very overworked and patient safety is on the line!!”<sup>1721</sup>
  - c. “I have never hated my job more than i do right now. The company has done ABSOLUTLEY NOTHING in recent years to show it cares anything about pharmacy and its employees. I see nothing but greed, no interest in the opinions of pharmacists, or patient safety. All company actions are in the interest of increasing profits. I would leave for another job tomorrow if I could.”<sup>1722</sup>
  - d. “inadequate pay for technicians is keeping your pharmacies understaffed. until you pay technicians the money they deserve this will not end, and by not paying them, you are pushing your pharmacists to their absolute limits both physically and mentally because we have to work with little to no staff and no breaks doing every task we are asked/required to do.”<sup>1723</sup>
  - e. “It is tireless work. I receive personal satisfaction from helping patients, but we are understaffed and underappreciated.”<sup>1724</sup>
  - f. “work used to be hard, but meaningful and doable. Now, I feel like Kroger could not care less about work conditions or patient care. They only see profit numbers.”<sup>1725</sup>
  - g. “I understand that the staffing supply is low, but the upper management seems to not care about anything not meeting metrics. Things are going to have to change otherwise major burnout will occur.”<sup>1726</sup>
  - h. “The lack of vision and the adoption of looking the other way has put pharmacy associates in a very precarious situation. The leadership has earned a vote of [“No Confidence”] from pharmacy associates.”<sup>1727</sup>
  - i. “the workload and 100% completion with accuracy and safety is not possible. the company is asking for mistakes to happen and they have happened! this is unsafe for patients and unsafe for the employees. all actions need to be corrected!”<sup>1728</sup>
  - j. “The work load is unrealistic and a danger to our patients”<sup>1729</sup>
3. Notably, the results from Kroger’s 2021 survey were similar to results from its 2018 survey of pharmacy staff. The 2018 pharmacy survey responses from pharmacy staff within Kroger’s Atlanta Division comprised almost 10% of all survey responses.<sup>1730</sup> Consistent with the 2021 survey, the results from Kroger’s 2018 pharmacy survey

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<sup>1721</sup> *Id.* (at Row 42)

<sup>1722</sup> *Id.* (at Row 324)

<sup>1723</sup> *Id.* (at Row 443)

<sup>1724</sup> *Id.* (at Row 1152)

<sup>1725</sup> *Id.* (at Row 1471)

<sup>1726</sup> *Id.* (at Row 1857)

<sup>1727</sup> *Id.* (at Row 2965)

<sup>1728</sup> *Id.* (at Row 3027)

<sup>1729</sup> *Id.* (at Row 3034)

<sup>1730</sup> Raney Dep. Exhibit 5, at Kroger-MDL00153735.

identified clear and significant problems with staffing, workload, training, and performance metrics.<sup>1731</sup>

#### **E. Transition to Heroin/Fentanyl/Xylazine**

1. The December 2013 Final Evaluation Report of the Cobb County Juvenile Family Reunification Program notes, “It appears that as jurisdictions have successfully curtailed access to prescription opiates through tighter monitoring and other strategies, the price of these drugs has increased substantially as their supply has dwindled. Individuals have as a result turned to heroin, which has become increasingly available and when compared to prescription opiates, rather more affordable.”<sup>1732</sup> Decreasing opioid prescribing was an important public health improvement, but large numbers of patients already addicted to prescription opioids had transitioned to illicit sources like heroin and illicit fentanyl.
2. In a September 2015 email, Major Vincent Hester of the Cobb County Sherriff’s Office M.C.S. Narcotics Unit reported that “Prescription pain sales on the street have slowed way down with the increase in heroin use...Early in 2015 we started to see combinations of Fentanyl and Heroin together, both in street drug buys and drug related deaths.”<sup>1733</sup> As overall opioid prescribing went down, illicit trading of prescription opioids on the street also decreased, illustrating the important linkage between the supply of prescription opioids and their diversion to illicit markets.
3. An April 2015 DEA Intelligence Report titled “Analysis of the Heroin Situation in the State of Georgia (2010-2014)” discusses informal behaviors like doctor-shopping and prescription fraud feeding opioid dependency in the area, “which has led some users to switch to heroin as a substitute.”<sup>1734</sup> When it becomes more difficult to obtain opioids from a doctor, patients already addicted often turn to illicit sources.
4. According to data from the Office of Health Indicators and Planning (OHIP), Georgia Department of Public Health, “While prescription opioid deaths declined last year [2015], users began shifting from prescription opioids to heroin. Hence, the spike in opioid deaths which include heroin.”<sup>1735</sup>

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<sup>1731</sup> Raney Dep. at 351:1-20.

<sup>1732</sup> COBBCO01508755 at 8777

<sup>1733</sup> COBBCO13305915

<sup>1734</sup> COBBCO07169761 at 9769

<sup>1735</sup> COBBCO08265464 at 5471

5. A key finding of the High Intensity Drug Trafficking Areas (HIDTA)<sup>1736</sup> 2017 Annual Report for the Atlanta-Carolinas<sup>1737</sup> region was that “The abuse and distribution of heroin in the AC-HIDTA region continues to be a major threat to the point that it has garnered attention of those in the public health sector because the users of heroin are generally prescription drug abusers.”<sup>1738</sup> Additionally, the Atlanta-Carolinas HIDTA’s 2016 Threat Assessment reported, “A significant contributing factor to the prescription drug abuse epidemic is the significant increase in the number of prescription written by physicians and dispensed by pharmacists.”<sup>1739</sup> The executive director of the Atlanta-Carolinas HIDTA, Daniel R. Salter, confirmed it is the position of the Atlanta-Carolinas HIDTA that there was a prescription drug abuse epidemic in 2016 and that pharmacists played a role in contributing to the prescription drug abuse epidemic.<sup>1740</sup>
6. The Cobb County Medical Examiner’s Annual report for 2015 reported, “During the end of 2014 and the beginning of 2015 there was an increase in deaths caused by heroin and fentanyl. This trend was in parallel with deaths throughout many regions of [Georgia].”<sup>1741</sup> The Annual Report for 2020 noted, “Fentanyl (and modified fentanyl) deaths were more than double in any prior year. The sharp increase in methamphetamine use in 2019, was further increased in 2020 to the highest levels in the past 6 years.”<sup>1742</sup> The Annual Report for 2021 (published October 2022) reported 30 accidental acute toxicity cases involving the combination of both methamphetamine and fentanyl, a higher number than in any prior year.<sup>1743</sup>
7. A local news investigation found a 4,000% spike in heroin-related deaths in an area they called “The Triangle” which included Marietta, GA and other parts of Cobb County<sup>1744</sup>.

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<sup>1736</sup> HIDTA is a grant program that provides assistance to “law enforcement agencies operating in areas determined to be critical drug-trafficking regions of the United States...At the local level, the HIDTAs are directed and guided by Executive Bards composed of an equal number of regional Federal and non-Federal (state, local, and tribal) law enforcement leaders...” DEA. 10 July, 2018. HIDTA. Retrieved from <https://www.dea.gov/operations/hidta> on 2 November, 2022

<sup>1737</sup> The Atlanta-Carolinas HIDTA region includes Cobb County.

<sup>1738</sup> Deposition of Daniel R. Salter. *In Re: National Prescription Opiate Litigation* (MDL No. 2804, Track 8). September 8, 2022 (herein after “Salter Dep.”), Exhibit 5 (ACHDTA\_0586) at ACHIDTA\_0598.

<sup>1739</sup> Salter Dep. Exhibit 4 (ACHIDTA\_0446) at ACHIDTA\_0498.

<sup>1740</sup> Salter Dep., at 201:7-12

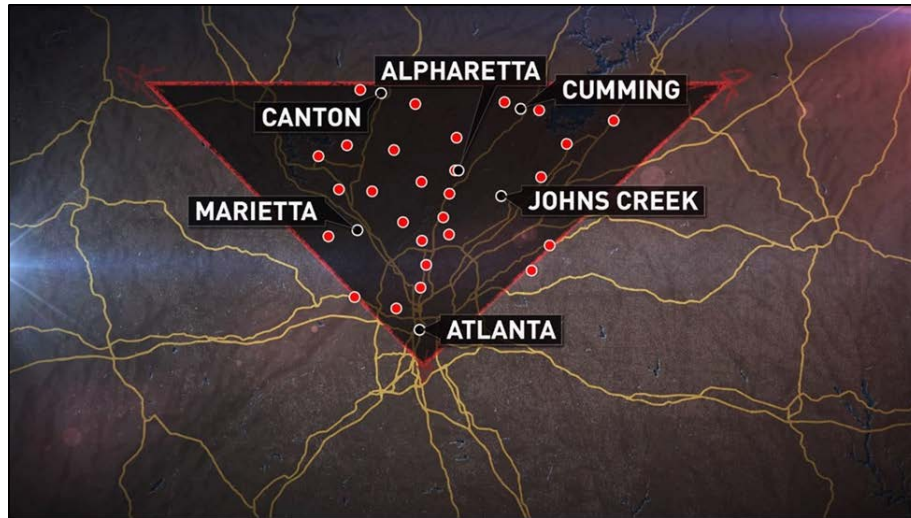
<sup>1741</sup> Cobb County Medical Examiner. 2015 Annual Report. April 2016, at 25.

<sup>1742</sup> Cobb County Medical Examiner. 2020 Annual Report. September 24, 2021, at 35.

<sup>1743</sup> Cobb County Medical Examiner. 2021 Annual Report. October 12, 2022, at 31.

<sup>1744</sup> What is “The Triangle”? (2017, March 2). *11 Alive*.

<https://www.11alive.com/article/news/investigations/triangle/what-is-the-triangle/85-68319931>



The same investigation reported on testimonies from the mothers of heroin users in “The Triangle,” including a mother who said her daughter began using prescription painkillers and then switched to heroin.<sup>1745</sup>

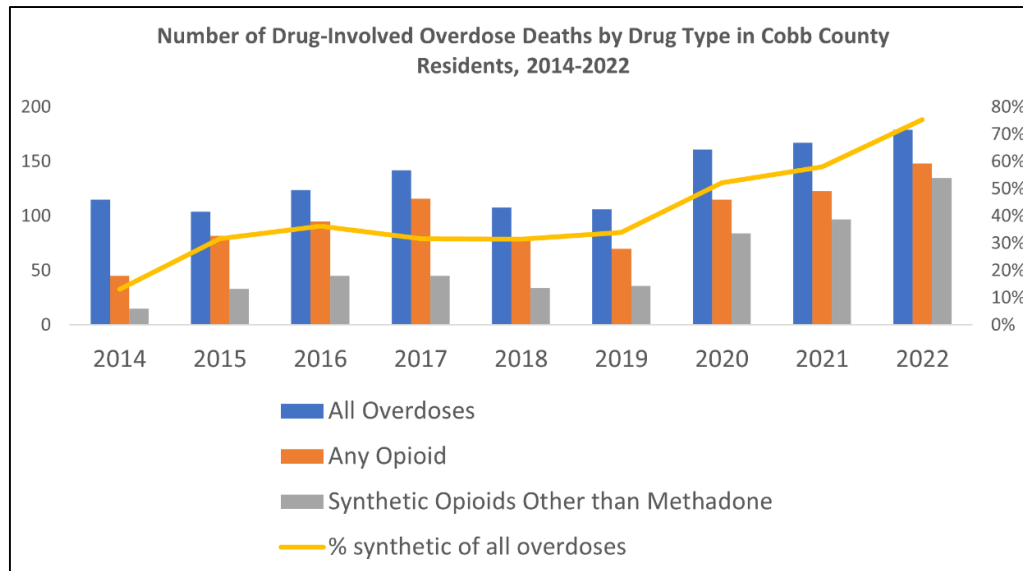
8. In August 2022, Cobb & Douglas Public Health (CDPH) warned that “Hospital Surveillance Data has found that over the last few months, fentanyl overdoses are spiking in Cobb and Douglas Counties.”<sup>1746</sup> Valerie Crow, spokesperson for CDPH, in discussing the spike, “gave as an example one part of Cobb that saw four emergency room visits for fentanyl-related incidents in a single week. That area of the county, she said, usually sees no more than one opioid-related emergency room visit in the same amount of time.”<sup>1747</sup> As shown in the graph below from CDPH, the percentage of overdoses caused by synthetic opioids (including fentanyl) rapidly rose from 2014 through 2022, with synthetic opioids accounting in 2022 for the vast majority of overdose deaths<sup>1748</sup>.

<sup>1745</sup> *Id.* at p. 8-12.

<sup>1746</sup> Crow, V. Cobb & Douglas Public Health. Fentanyl Overdoses Spiking, in Cobb and Douglas Counties, August 12, 2022. <https://www.cobbanddouglaspublichealth.com/2022/08/fentanyl-overdoses-spiking-in-cobb-and-douglas-counties/>

<sup>1747</sup> Busch, J. (2022, August 17). Cobb sees spikes in fentanyl overdoses. *Marietta Daily Journal*. [https://www.mdjonline.com/news/local/cobb-sees-spikes-in-fentanyl-overdoses/article\\_65676e90-1da5-11ed-8fc1-3b92fcf28575.html](https://www.mdjonline.com/news/local/cobb-sees-spikes-in-fentanyl-overdoses/article_65676e90-1da5-11ed-8fc1-3b92fcf28575.html)

<sup>1748</sup> Cobb & Douglas Public Health. *Opioid Data*. <https://cobbanddouglaspublichealth.com/programs/opioid-response/opioid-data/>



9. The increase in fentanyl overdoses in Cobb County mirrors a “surge of overdoses” in Georgia caused by illegal drugs laced with fentanyl.<sup>1749</sup> The Georgia Bureau of Investigation (GBI) reported “a significant increase” in fentanyl and a rise in overdose clusters, opioid-related deaths, and seizures of fentanyl. A spokesperson for the GBI also notes a “disturbing trend of samples called ‘purple heroin/purp’ that contains heroin and fentanyl.”<sup>1750</sup> The Cobb County Sheriff’s Office also warned about “purple heroin” circulating in Cobb County.<sup>1751</sup>
10. Overdose deaths involving fentanyl increased 800% from 2019 to 2021 among Georgia adolescents (10-19 years), 3.7 times more than adults.<sup>1752</sup> In addition, from 2019 to 2021 death involving any opioid increased 236% among Georgia adolescents.<sup>1753</sup> As shown in the graph below<sup>1754</sup>, for both adolescents and adults, the proportion of overdose deaths involving fentanyl has grown significantly since 2019:

<sup>1749</sup> Miller, A. (2022, April 4). Fentanyl-related overdoses surge in state. *Georgia Public Broadcasting*. <https://www.gpb.org/news/2022/04/04/fentanyl-related-overdoses-surge-in-state>

<sup>1750</sup> *Id.*

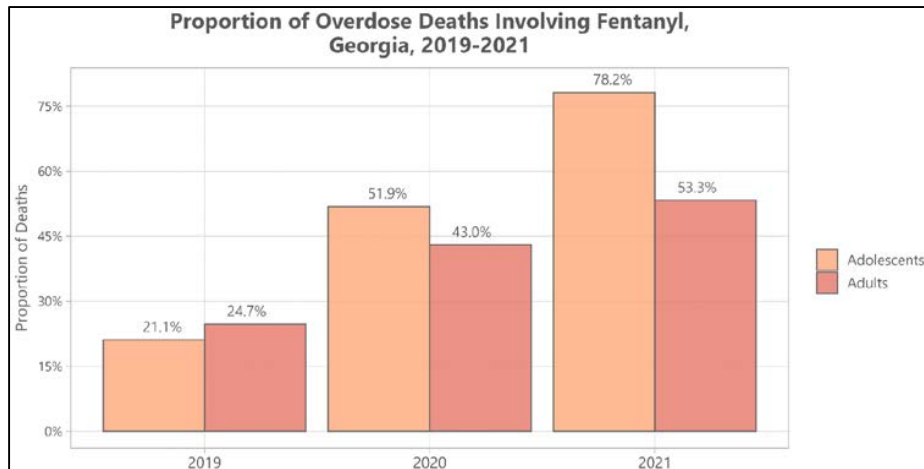
<sup>1751</sup> Jackson, R. (2022, September 9). Authorities warn of new deadly 'rainbow fentanyl' pills, powder as drug circulates in Georgia. *11 Alive*. <https://www.11alive.com/article/news/local/rainbow-fentanyl-authorities-warn-of-deadly-and-colorful-drug/85-79a4cfbc-212c-46d6-85d0-2877a868ed62>

<sup>1752</sup> Georgia Department of Public Health. (2022, September 1). *Overdose Deaths Among Adolescents, Georgia, 2019-2021*. <https://dph.georgia.gov/document/document/adolescent-opioid-report-9822/download>, at p.2.

<sup>1753</sup> *Id.*

<sup>1754</sup> *Id.* at p. 3.





11. A 2023 publication of the Georgia Department Health noted a recent increase in the presence of xylazine in overdose deaths.<sup>1755</sup> Significantly, in 100% of the suspected xylazine-involved deaths, fentanyl was also present;<sup>1756</sup> fentanyl use, in turn, was an outgrowth of the prescription opioid epidemic.

## F. Conclusion

Cobb County has been severely impacted by the opioid epidemic, which began with the misrepresentations of safety and efficacy of prescription opioids, combined with ubiquitous distribution and dispensing. With specific regard to the role of pharmacies, the Georgia Pharmacy Association found Georgia pharmacists are overworked to the point of concern about patient safety,<sup>1757</sup> making it impossible for their pharmacists to exercise their corresponding responsibility as the last line of defense against the opioid oversupply, which caused the opioid epidemic. As elsewhere, the epidemic of prescription opioids gave rise to the second and third waves of heroin and fentanyl epidemics. As the availability of prescription opioids decreased and their cost increased, the greater availability, lower cost, and increased potency of heroin and illicit fentanyl maintained and/or accelerated the addiction of many who were already addicted to and/or dependent on prescription opioids.

<sup>1755</sup> Georgia Department of Public Health. (2023). *Xylazine-Involved Drug Overdose Deaths Georgia, 2020-2022*. <https://dph.georgia.gov/document/document/xylazine-involved-overdose-deaths-final3823pdf/download>

<sup>1756</sup> *Id.*

<sup>1757</sup> Davidson, M. (2022, February-March). Toxic Work Environments. *Georgia Pharmacy*, 31.

*Lembke Report*

*Confidential — Subject to Protective Order*

## Anna Lembke, M.D. Report

# APPENDIX IV

Statement of Anna Lembke, MD on the Proper Indication for Opioids

**Appendix IV: Statement of Anna Lembke, MD on the Proper Indication for Opioids****A. Chronic Noncancer Pain (CNCP)**

The recent, authoritative report of the National Academy of Science, Engineering and Mathematics (NASEM) concluded that “*available evidence does not support the long-term use of opioids for management of chronic noncancer pain*. On the other hand, evidence indicates that patients taking opioids long-term are at increased risk of OUD and opioid overdose, as well as a number of other adverse outcomes.”<sup>1758</sup> I concur.

Prescription opioids are not recommended in the treatment of chronic pain. A growing body of evidence demonstrates serious risks of harm with long-term opioid use, made worse with increasing dose and duration. Further, there is no reliable evidence for efficacy of opioids in the treatment of pain beyond 12 weeks.<sup>1759</sup> In short, long-term opioid therapy for chronic pain is contrary to the evidence and not good medical practice.

A large and growing body of evidence shows dose and duration-dependent harms caused by chronic opioid therapy, including but not limited to addiction and death.<sup>1760</sup> Further, opioids can make pain worse over time through a process called opioid induced hyperalgesia, which is closely linked to neuroadaptation and tolerance.

The claims of benefits of long-term opioids for chronic pain are based on low quality, anecdotal evidence, and contrary to the randomized controlled trial (RCT) evidence and consensus views. A recent meta-analysis by Busse, *et al.*, assessed available RCTs of opioids, finding that compared to placebo, the difference in pain relief did not meet a pre-specified “Minimally Important Difference” (MID), defined as “the smallest amount of improvement in a treatment outcome that patients would recognize as important.”<sup>1761</sup> Nevertheless, the authors stated that approximately 12% percent of chronic pain patients might choose to evaluate whether, in their individual experience, opioids might provide improved pain relief compared to other medications, despite the known, increased risk of opioids, an assertion that is not supported by their data.<sup>1762</sup>

The NASEM Report’s conclusion was subsequently reinforced by the 2018 publication of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) study in the *Journal of the American Medical Association*, by Krebs, *et al.* As the only long-term, RCT of chronic opioid therapy compared to non-opioid pain medications, it provides the best available evidence on the subject. The SPACE trial found that non-opioid medications (for example nonsteroidal anti-inflammatory drugs

<sup>1758</sup> NASEM (2017), fn. 58, above, at p.51 (emphasis added).

<sup>1759</sup> A single RCT of oxycodone and morphine versus placebo was carried out for 16 weeks. Jamison RN, Raymond SA, Slawsky EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine* (Phila Pa 1976). 1998;23(23):2591-2600. doi:10.1097/00007632-199812010-00014.

<sup>1760</sup> See, e.g., Bohnert *et al.* “Association Between Prescribing Patterns,” fn. 1467, above; Dunn, *et al.* “Opioid Prescriptions,” fn. 1560, above.

<sup>1761</sup> Busse *et al.* “Opioids for Chronic Noncancer Pain,” fn. 1139, above.

<sup>1762</sup> According to the CDC, approximately 3-4% of prescription opioid users take these drugs for long-term treatment of pain. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;15(15):1624–1645. Therefore, the number of opioid users who might choose to evaluate whether opioids provide greater pain relief would be 12% x of the approximately 3.5% who use opioids for chronic pain, or 0.4% of all opioid users.

such as naproxen or acetaminophen) provide equivalent or greater pain relief compared to opioids, while opioids confer significantly greater risks, leading Krebs *et al.* to conclude that chronic opioid therapy is not advisable.<sup>1763</sup>

A 2017 Veterans Administration/Department of Defense guideline stated, “We recommend *against* initiation of long-term opioid therapy for chronic pain. (Strong against).”<sup>1764</sup> ...Based on the evidence, it was considered that *opioid therapy should no longer be given when all nonopioid approaches fail due to the substantial risk of harms.*<sup>1765</sup> The VA/DoD guideline was “largely driven by the risk for development of opioid use disorder,” and found “little evidence of benefit for long-term opioid use.”<sup>1766</sup> A 2022 update went further, stating that: “Compared with the 2017 recommendation against initiation of *long-term* opioid therapy, the updated recommendation against opioid therapy in general for chronic pain is broader and reflects the evidence that opioid therapy for any duration is harmful.”<sup>1767</sup>

As a clinician, I have treated hundreds of patients with chronic pain for associated conditions of opioid misuse, dependence, and OUD. My experience is consistent with the authorities referenced above, in that the claimed benefits of long-term opioid therapy for chronic pain do not outweigh the risks; to the contrary, when patients successfully followed a compassionate, patient-centered tapering program to reduce or cease opioid therapy, they reported improvement in their overall well-being and level of pain, and none reported worsening of pain except for the pain of withdrawal from the opioids themselves, which was time-limited.

Based on the consensus view stated in the NASEM Report, research findings, and my own clinical experience, it is my view that at a population level, the risks of long-term opioids for chronic pain far outweigh the benefits. For very few patients, benefits might outweigh the risks; but even then risks increase with higher dose and longer duration of opioid treatment, such that risks may eventually exceed any small possible benefit over other less dangerous pain reduction strategies.

## **B. Whether or Not Pain is “Undertreated,” Opioids Are Not the Solution**

The epidemic of opioid over-prescribing in the past 25 years was fueled, in part, by industry assertions that chronic pain was “undertreated” in the United States. On this subject, I agree with the conclusion in the NASEM Report: “The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but *it would be a mistake to infer that greater utilization of opioids would ameliorate these problems.*”<sup>1768</sup> This conclusion follows directly from NASEM’s conclusion that evidence does not support

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<sup>1763</sup> Krebs, “Effect of Opioid vs Nonopioid Medications”, fn. 1181, above, at p.872.

<sup>1764</sup> Rosenberg, JM, *et al.* “Opioid Therapy for Chronic Pain: overview of the 2017 US Department of Veterans Affairs and US Department of Defense clinical practice guidelines”, fn. 1202, above, at p. 930 (emphasis added).

<sup>1765</sup> *Id.* (emphasis added)

<sup>1766</sup> *Ibid.*

<sup>1767</sup> Sandbrink, “The Use of Opioids”, fn. 1180, above, at p. 389.

<sup>1768</sup> NASEM Report (2017), fn. 58, above, at p. 51. (emphasis added).

efficacy of long-term opioids for chronic pain, while the risks of such therapy are significant and well-established.

There are many estimates of the prevalence of chronic pain in the United States, which vary depending on the definitions of the investigators. A reasonable, recent estimate is found in an article by Pitcher, *et al.*, sponsored by the National Institutes of Health as a part of the “National Pain Strategy” (NPS), which reported overall Chronic Pain at 18.4%, and High Impact Chronic Pain (HICP) at 4.8%.<sup>1769</sup> The NPS defines HICP as the experience of pain on most days over the past 3 months, with concomitant limitations on activities due to pain. To the extent that long-term opioid therapy would ever be warranted, it is my opinion that only the severity of HICP might justify imposing the known risks of long-term opioid treatment.

### **C. Tapering Is Appropriate for Opioid Dependence and OUD**

After nearly three decades of opioid overprescribing, we now find ourselves in the lamentable situation wherein millions of Americans are physiologically dependent on opioids, some of whom may never be able to taper down and/or off of opioids, due to irreversible neuroadaptation. The most compassionate approach to these patients is a slow, patient-centered opioid taper.<sup>1770</sup> In cases of severe prescription opioid dependence where opioid tapering fails, continuing opioids at low and closely monitored doses may be the most compassionate harm-reduction approach.<sup>1771</sup>

### **D. Non-opioids Have Been Found to Be Equivalent or Superior to Opioids in Many Acute Pain Settings**

Opioids are indicated for short-term use (days to weeks, up to 90 days) in the management of acute pain (*e.g.*, trauma, dental procedures, and post-surgery). However, there are numerous studies finding that non-opioids provide equivalent pain relief with lower risk. For example, a 2018 study of dental pain by Moore, *et al.*, found non-opioids superior to opioids: “The best available data suggested that the use of nonsteroidal medications, with or without acetaminophen, offered the most favorable balance between benefits and harms, optimizing efficacy while minimizing acute adverse events.”<sup>1772</sup> The Moore study supports that opioids are not an appropriate choice for dental pain, according to evidence-based principles comparing risks and benefits. Nonetheless, a recent survey found that 23% of patients who received an opioid prescription in a one-year period were prescribed opioids by a dentist or oral surgeon.<sup>1773</sup>

<sup>1769</sup> Pitcher MH, Von Korff M, Bushnell MC, Porter L. Prevalence and Profile of High-Impact Chronic Pain in the United States. *J Pain*. 2019;20(2):146-160. doi:10.1016/j.jpain.2018.07.006.

<sup>1770</sup> Lembke, “BRAVO! A Collaborative Approach to Opioid Tapering.”, Oregon Pain Guidance, March 2020, <https://www.oregonpainguidance.org/wp-content/uploads/2020/03/BRAVO-FINAL-3.13.20-1.pdf>

<sup>1771</sup> Chou, R., Ballantyne, J., Lembke, A., “Rethinking Opioid Dose Tapering”, fn. 19, above.

<sup>1772</sup> Moore, *et al.*, Benefits and harms associated with analgesic medications used in the management of acute dental pain. 2018; 149: 256-263, *J Am Dental Assoc*. 2018; 149: 256-265.

<sup>1773</sup> Press Release: One-Third of Americans Have Received an Opioid Prescription in the Past Two Years, NORC at the University of Chicago, September 27, 2018.

A 2023 randomized, placebo-controlled trial of opioid analgesia for acute low back and neck pain concluded that “Opioids should not be recommended for acute non-specific low back pain or neck pain given that we found no significant differences in pain severity compared with placebo.”<sup>1774</sup>

Opioids are also commonly prescribed for the pain of acute trauma in emergency medicine. However, the results of a recent study of opioids and non-opioid pain relievers in emergency care concluded that “there are no clinically meaningful differences between the analgesic effects of these 4 analgesics and suggest that a combination of ibuprofen and acetaminophen represents an alternative to oral opioid analgesics for the treatment of acute extremity pain in the ED,” and that nonopioid patients experienced greater pain relief with fewer adverse events.<sup>1775</sup>

In the context of post-surgery treatment, numerous studies have found that non-opioids can be substituted for opioids, or that the number of opioids prescribed post-surgery can be substantially reduced, with equivalent pain relief. For example, in a study in which patients were treated with Tylenol/ibuprofen after parathyroid and thyroid surgery, the authors concluded that such patients “need very little, if any, post-operative opioids.... Decreasing the volume of opioid medications prescribed at discharge will decrease waste and reduce potential for addiction.”<sup>1776</sup> Other authors stated, “we have completely stopped prescribing opioids” for cervical neck operations, and reduced Norco (acetaminophen + 5mg hydrocodone) prescribing from 40 pills down to 5 pills for adrenalectomy, finding that non-opioid medications provided comparable pain relief; they concluded that perioperative and post-surgery opioid use is “less about inherent pain associated with operations, but more about misperceptions and biases that both physicians and patients have about post-operative pain and required management.”<sup>1777</sup> A study by Mian *et al* shows that even major surgeries (“major urologic cancer surgery”) can be accomplished with a restrictive opioid protocol without a significant increase in patients’ reports of pain.<sup>1778</sup> The authors write, “This perioperative protocol, with emphasis on nonopioid alternatives and patient instructions, may be safe and effective in nearly eliminating the need for opioid prescriptions after major abdominopelvic cancer surgery without adversely affecting pain control, complications, or recovery.”<sup>1779</sup>

Based on the state of scientific inquiry, the CDC has found the evidence sufficient to support the conclusion that naproxen, an NSAID, is as effective as opioids for acute pain, and with lower risk of adverse effects.<sup>1780</sup>

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<https://www.norc.org/NewsEventsPublications/PressReleases/Pages/one-third-of-americans-have-received-an-opioid-prescription-in-the-past-two-years.aspx>

<sup>1774</sup> Jones, “The OPAL trial”, fn. 1222, above, at p. 1.

<sup>1775</sup> Chang, “Effect of a Single Dose of Oral Opioid,” fn. 1505, above.

<sup>1776</sup> Shindo, “Opioid Prescribing Practice and Needs” fn. 1501, above, at p. 1102.

<sup>1777</sup> Kuo, “Use and Misuse of Opioids,” fn. 1486, above.

<sup>1778</sup> Mian, B. M., Singh, Z., Carnes, K., Lorenz, L., Feustel, P., Kaufman, R. P., Jr, Avulova, S., Bernstein, A., Cangero, T., & Fisher, H. A. G. (2023). Implementation and Assessment of No Opioid Prescription Strategy at Discharge After Major Urologic Cancer Surgery. *JAMA Surgery*, e227652. Advance online publication. <https://doi.org/10.1001/jamasurg.2022.7652>

<sup>1779</sup> *Id.* at p. E1.

<sup>1780</sup> Opioids for Acute Pain: Get the Facts, Ctrs. for Disease Control and Prevention. <https://www.cdc.gov/drugoverdose/pdf/patients/Get-the-Facts-a.pdf>



**E. Risk of Persistent Use following Opioids for Acute Pain**

There is a consensus that opioids for acute pain lead to persistent use among 10 to 30% of short-term users, and there is significant concern over such persistent use after initiating conditions have abated.<sup>1781</sup> This subset of patients receives no benefit from continued opioid use, since the initiating painful condition is no longer in need of treatment; instead, such patients have become dependent and are at increased risk of OUD and mortality due to the known exacerbation of risk with longer duration of exposure. A recent study found that the risk of persistent use of opioids after surgery was dramatically reduced by a protocol that (a) limited the number of opioids prescribed at discharge and (b) recaptured the vast majority of unused pills.<sup>1782</sup> The authors suggested these common-sense steps to reduce the risk of opioid dependence and addiction after surgery.

**F. Over-prescribing for Acute Pain Is a Source of Diversion**

Additional harms of overprescribing for acute pain arise from the fact that patients commonly do not use all of the pills prescribed for their condition, since they are not needed for pain relief, or because of adverse side effects. The unused pills become a source of sale, gift, theft, or barter, to individuals for whom the drugs were not prescribed, and who are by definition misusing the opioids to maintain a habit, or to get high.<sup>1783</sup>

**G. Opioid Use for Specific Painful Disease States**

Opioids are indicated for treatment of certain painful diseases (*e.g.*, sickle cell crisis, post-herpetic neuralgia (PHN)),<sup>1784</sup> end-of-life suffering (hospice care). Opioids are also indicated for cancer pain, based in significant part on the expectation that cancer patients have a limited life expectancy, and that the risks of Opioid Use Disorder (OUD) and mortality are outweighed by the benefits of pain relief. However, with advanced treatment methods, more cancer patients are surviving for longer periods of time, and the risks of addiction and overdose mortality among cancer patients have been identified in the peer-reviewed medical literature<sup>1785</sup> Thus, even in the setting of cancer pain, caution

<sup>1781</sup> See, *e.g.*, Deyo, “Use of Prescription Opioids,” fn. 1492, above, at p. 5 (13% persistent users); Cook, “Benchmarks of Duration and Magnitude,” fn. 1495, above, at p. 638 (10-13%) and Johnson, “Prescription quantity and duration,” fn. 1307, above, at p. 1. (29.9%)

<sup>1782</sup> Barth R, *et al.* Reasons for long-term opioid prescriptions after Guideline-directed opioid prescribing and excess opioid pill disposal. *Annals of Surgery*. 2023;277(1):173-178.

<sup>1783</sup> NASEM (2020), fn.1498, above, at p.26.

<sup>1784</sup> Sickle cell disease affects 100,000 Americans, and 1 of every 365 Americans of African descent. Data & Statistics on Sickle Cell Disease, Ctrs. For Disease Control and Prevention, <https://www.cdc.gov/ncbddd/sicklecell/data.html> (last reviewed October 21, 2019) Approximately 1 million cases of herpes zoster (HZ, or “shingles”) occur annually in the US; it is estimated that 5%–20% of those with HZ go on to develop PHN. Malick-Searle, Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *Journal of Multidisciplinary Healthcare* 2016;9 :447–454.

<sup>1785</sup> For example, the Bohnert study found a hazard ratio (HR) of 11.99 for opioid-associated mortality among cancer patients exposed to 100 mg MME opioids, compared to those exposed to 1-20 mg, and this HR exceeded even the significantly elevated HR for patients with acute and chronic pain conditions. Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 1315.

should be exercised to treat with the lowest dose for the shortest time, and to treat with low dose opioids intermittently rather than continuously, to reduce the risks of OUD and mortality.

## **H. Conclusion**

The adverse effects of opioids are well-known and devastating. These include dependence, opioid use disorder (OUD)/addiction, overdose mortality, primarily due to respiratory suppression, non-fatal overdose, and neonatal abstinence syndrome (NAS), which afflicts newborns well into childhood. These conditions are severe, fatal or life-threatening, permanent or of long duration.

In contrast, the benefits of prescription opioids are limited or ephemeral. I agree with the consensus of leading authorities that there is no reliable evidence that long-term opioids provide clinically significant relief of CNCP, and the best evidence supports equivalent pain relief and fewer risks with non-opioids such as NSAIDs. Although opioids are indicated for acute pain, numerous studies show equivalent relief and lower risk with non-opioids; a significant minority of acute-pain opioid patients go on to become persistent users who suffer dependency but do not benefit from opioid use; over-prescribing for acute conditions results in diversion to inappropriate users, a source of community harm that further offsets any pain relief benefits to appropriate users; and the pain relief in acute conditions is inherently brief, compared to the long-term or permanent harms of fatal and non-fatal overdose, OUD and NAS.

In summary, it is my opinion that the harms of prescription opioids far outweigh any benefits that may be conferred.

*Lembke Report*

*Confidential — Subject to Protective Order*

# Anna Lembke, M.D. Report

## APPENDIX V

### Summary of BRAVO Protocol

## **Appendix V: Summary of BRAVO Protocol**

### **Broaching the Subject**

- Involve the patient
- Take more time
- Get the support of your team
- Use motivational interviewing (reflection, validation, support)
- For inherited patients, maintain the current dose and document if considering a taper

### **Risk Benefit Assessment**

- Consider tapering for the following reasons:
- Patient request
- Pain and function not improved
- Adverse opioid effects
- Co-occurring conditions (including mental health)
- Dose over 90 MED
- Concurrent sedatives
- Opioid use disorder
- Opioid overdose

### **Addiction and Dependence Happen**

- Addiction = The 3 C's: *Control, Craving*, continued use despite *Consequences*
- Dependence = Tolerance, withdrawal, without the 3 C's
- Anyone can become addicted or dependent
- Reassure patients there is effective treatment for both
- Consider buprenorphine

### **Velocity and Validation**

- Go slowly (*Tapering Examples*)
- Maintain the same schedule (BID, TID)
- Let the patient drive "*Which opioid would you like to taper first?*"
- Take breaks, but never go backwards
- Warn patients that pain gets worse before it gets better
- Validate that opioid tapering is hard

### **Other Strategies for Coping with Pain**

- Help patients understand how pain works
- Encourage regular, restful sleep
- Promote healthy activities
- Maintain a positive mood
- Foster social connections
- Make good nutritional choices
- Consider non-opioid pain medications

*Lembke Report*

*Confidential — Subject to Protective Order*

# Anna Lembke, M.D. Report

## EXHIBIT A

Curriculum Vitae and List of Publications

**Anna Lembke, M.D.**

Professor of Psychiatry and Behavioral Sciences  
Medical Director of Addiction Medicine  
Stanford University School of Medicine  
Department of Psychiatry and Behavioral Sciences  
401 Quarry Road, Stanford, CA, 94305  
Office: 650 725-9570 Fax: 650 725-8048  
alembke@stanford.edu

**Education and Training**

1985-1989	Yale University (BA, Humanities; <i>summa cum laude</i> ) New Haven, CT
1989-1990	University of Beijing (Mandarin Chinese) Beijing, China
1992-1995	Stanford University School of Medicine (MD) Stanford, CA
1995-1997	Residency, Pathology Stanford University School of Medicine, Stanford, CA
1997-1998	Internship, Internal Medicine Highland Hospital, Alameda, CA
1998-2000	Residency, Psychiatry Stanford University School of Medicine, Stanford, CA
2000-2002	Fellowship in Mood Disorders, Psychiatry and Behavioral Sciences Stanford University School of Medicine, Stanford, CA

**Honors and Awards**

1989	<i>Summa cum laude</i> in Humanities Yale University
1989	Outstanding Contributor to Community Life Yale University
1989	Yale-China Fellowship Yale University
1995	Outstanding Teacher in Structural Biology Stanford University School of Medicine



1999	Outstanding Research in Severe Mental Illness Janssen Scholar
2000	Travel Scholarship Medical Education and Research Foundation (MERF)
2000	Outstanding Research in Severe Mental Illness American Psychiatric Association
2002	Laughlin Fellowship American College of Psychiatrists
2009	Travel Scholarship Alcohol Medical Scholars Program
2011	Travel Scholarship Association of Medical Education, Research, Substance Abuse
2013	Faculty Fellowship Stanford University School of Medicine
2014	Excellence in Academic Teaching Stanford University School of Medicine
2015	Chairman's Clinical Innovation Award Stanford University School of Medicine
2017	Distinguished Visiting Professorship Johns Hopkins Bayview, Department of Internal Medicine
2018	Distinguished Flexner's Dean Lecturer Vanderbilt University School of Medicine
2018	Distinguished Marcel Malden Lecturer Tacoma, Washington
2018	Distinguished Alpha Omega Alpha Visiting Professorship University of Kansas School of Medicine
2018	Distinguished Alumni Award Evanston Township High School, Evanston, IL
2018	Excellence in Academic Teaching Award Stanford University School of Medicine

2019	Distinguished Baldwin Lecturer The Accreditation Council for Graduate Medical Education (ACGME)
2019	Distinguished Tector Lecturer 69th Annual Course for Family Physicians, Montreal, Canada
2019	Distinguished James Platt White Memorial Lecturer Buffalo, New York OB/GYN Society
2019	Distinguished Crowley Lecturer Lucile Packard Children's Hospital, Stanford University
2019	Distinguished University of Tampa Honors Symposium Lecturer University of Tampa, Florida
2019	Distinguished Evelyn G. Keever Bioethics Day Lecturer Eastern Virginia Medical School
2020	Fellowship Training Directors Award American Society of Addiction Medicine
2020	Irma Bland MD Certificate of Excellence in Teaching Residents American Psychiatric Association
2021	Distinguished Alpha Omega Alpha Visiting Professorship University of Nevada, Reno School of Medicine
2021	Hazelden Betty Ford Foundation Humanitarian Award Hazelden Betty Ford Foundation, Rancho Mirage, California
2022	Chairman's Polymath Award Stanford University School of Medicine
2022	Distinguished Freedman Memorial Lecturer University of Chicago
2022	Distinguished Callahan Lecturer Case Western Reserve University
2023	Distinguished Reeves Warm MD Lecturer University Hospitals, Cleveland, Ohio
2023	38 <sup>th</sup> Distinguished Feldman Lecturer Edmonton, Alberta, Canada

**Academic and Clinical Appointments, Stanford University**

2003-2010     Instructor Department  
Department of Psychiatry and Behavioral Sciences (9/03-4/10)

2010-2017     Assistant Professor  
Department of Psychiatry and Behavioral Sciences (5/10-4/17)

2012-present   Chief, Addiction Medicine Dual Diagnosis Clinic  
Department of Psychiatry and Behavioral Sciences

2013-2018     Founding Program Director, Addiction Medicine Fellowship  
Department of Psychiatry and Behavioral Sciences  
Accredited by the American Board of Addiction Medicine

2018-present   Founding Program Director, Addiction Medicine Fellowship  
Department of Psychiatry and Behavioral Sciences  
Accredited by ACGME

2016-2021     Courtesy Appointment  
Department of Anesthesiology and Pain Medicine

2017-present   Medical Director, Addiction Medicine  
Stanford Health Care and Stanford University Hospital

2017-2021     Associate Professor  
Department of Psychiatry and Behavioral Sciences (7/17-6/21)

2020-present   Director (Interim), Taube Youth Addiction Initiative  
Department of Psychiatry and Behavioral Sciences

2021-present   Professor of Psychiatry and Behavioral Sciences  
Department of Psychiatry and Behavioral Sciences

**Other Previous Employment**

1991-1992     Bilingual Teacher (grades K-8), State Certified in Chinese (Mandarin)  
Healy Elementary School, Chicago, IL

1989-1990     English Teacher, Yali Middle School  
Changsha, China

**Medical Licensure and Specialty Board Certification**

1995             California medical license #A62241

- 2003           Diplomate, American Board of Psychiatry and Neurology  
Certificate #51988; recertified 2/18/2013
- 2012           Diplomate, American Board of Addiction Medicine  
Certificate #2012288; certified 12/15/2012 -12/31/2022
- 2013           DEA-X waived to prescribe buprenorphine products
- 2021           Diplomate, American Board of Preventive Medicine; Certificate #61-  
17111; certified 01/01/2021 - Exp date 12/31/2030

**Educational Leadership, Stanford University**

- 2003-2005     Chair, Curriculum Committee  
Department of Psychiatry and Behavioral Sciences  
Stanford University School of Medicine
- 2009-present   Course Director, CME-accredited monthly Stanford seminar series for  
community physicians - “Closing the Gap: Moving towards Best Practices  
in Psychiatry”
- 2012-2014     Principal Organizer and Lecturer of the free Buprenorphine Certification  
Course and CURES registration for Stanford University
- 2013-present   Program Director, Addiction Medicine Fellowship  
Department of Psychiatry and Behavioral Sciences  
Stanford University School of Medicine
- 2014           Expert Consultant, Alcohol and Women Task Force  
Office of the Vice Provost for Student Affairs, Stanford University
- 2014-2016     Annual Medical Student Town Hall Meetings on Wellness and  
Professionalism (Issues of Substance Use and Addiction)  
Office of the Dean of the School of Medicine, Stanford University
- 2015-2016     Expert Consultant, Alcohol and Other Drug (AOD) Subcommittee of the  
Mental Health and Well-Being Advisory Committee  
Stanford University
- 2016-present   Chair, Addiction Medicine Task Force  
Stanford University School of Medicine  
(Goal: create a new curriculum for addiction/safe opioid prescribing)
- 2017-2022     Committee on Professionalism  
Stanford University School of Medicine

2021-present Collegiate Recovery Advisory Committee  
Stanford University

**Teaching and Mentoring, Stanford University**

2002-present Course Director, Addiction Medicine, Stanford University School of Medicine

2009-present Course Director, Stanford CME series “Closing the Gap in Psychiatry”

2012-present Course Lecturer, Substance Use Disorders, Stanford Child Psychiatry Fellowship

2012-2020 Course Lecturer, Substance Use Disorders, Stanford Palliative Care Fellowship

2012/’14/’16 Biennial lecture on addiction medicine to Stanford undergraduates as part of the Hum Bio Molecular and Cellular Physiology 256 seminar

2021-present Course Lecturer on Addiction, Stanford undergraduate Psychology 101

**Clinical Supervision (weekly year round), Stanford University**

2002-2018	Inpatient Psychiatry	Med Students, Residents, Fellows
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2010-present	Addiction Med/Dual Dx Clinic	Med Students, Residents, Fellows
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2013-2018	Pain and Addiction Clinic	Pain Fellows
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**Addiction Medicine Fellowship, Director, Stanford University**

2013-14	Stacie Solt, MD, Emergency Medical and Addiction Medicine, now at San Mateo Medical Center, San Mateo, CA
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2014-15	Mitika Kanabar, MD, Family Medicine Physician and Addiction Medicine, now at Southern California Permanente Medical Group, Lancaster, CA
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2015-16	Chinyere Ogbonna, MD, Family Medicine, Psychiatry, and Addiction Medicine, now Medical Director of Chemical Dependency Services at Kaiser Permanente, San Jose, CA
---------	--

2016-17	Rachel Sussman, MD, Family Medicine and Addiction Medicine, now Assistant Professor at Stanford School of Medicine and Indian Health Center/O’Connor, San Jose, CA
---------	--

- 2017-18 Amer Raheemullah, MD, Internal Medicine and Addiction Medicine, now Assistant Professor and Director of the Inpatient Addiction Medicine Consult Service at Stanford School of Medicine, Stanford, CA
- 2017-18 Anusha Chandrakanthan, MD, Family Medicine and Addiction Medicine, now Adjunct Clinical Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA, and Staff Physician at Valley Homeless Health, San Jose, CA
- 2018-19 Huiqiong Deng, MD, PhD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA
- 2018-19 Michael Polignano, MD, Psychiatry and Addiction Medicine, now Assistant Professor in Addiction Medicine at Stanford University School of Medicine, Stanford, CA
- 2019-20 Ori Benhamou, MD, Psychiatry and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2019-20 Nathaniel Lepp, MD, Family Medicine and Addiction Medicine, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2020-2021 Matilde Fredrickson, DO, Warren Yamashita, MD, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2021-2022 Hussain Abdullah, MD, Thomas Bottyan, MD, Sara Cohen-Fournier, MD Jasser Khairallah, DO, Depinder Singh, MD, Steven Tate, MD, Lucia Tome, MD, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2022-2023 Martin Binesh, MD, Bailee Jacobsen, DO, Henry Moss, DO, Mastaneh Nikravesh, MD, Gabriela Ruchelli, MD, Stanford Addiction Medicine Fellowship, Stanford, CA
- 2023-2024 Nicolas Garel, MD, Asaf Jacobs, MD, Connie Chen, MD, Diana Chen, MD, Steven Marabondo, MD, Nicole Steinmuller, MD

**MedScholars Advisor, Stanford University**

- 2016 MedScholar Advisor for Inbar Raber, *Qualitative Assessment of Clerkship Students' Perspectives of Pain and Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California
- 2017 MedScholar Advisor for Alex Ball, *Developing the Addiction Curriculum at Stanford*, Stanford University School of Medicine, Stanford, California



2019 MedScholar Advisor for Emily Keamy-Minor, *Alcohol Screening for Patients Receiving Prescriptions for Benzodiazepines and Opioids*, Stanford University School of Medicine, Stanford, California

**Dissertation/Masters Review Committees, Stanford University/Palo Alto Consortium**

2016 Dissertation Advisor and Review Committee Member for Jennifer Bielenberg, *Addiction and Stigma*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2017 Dissertation Chair and Review Committee Chair for Shelby Schwartz, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2018 Dissertation Chair and Review Committee Chair for Julia Yasser, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2020 Dissertation Committee, Sarah Krasner, *Gender Differences in Cannabis Vaporizer Use*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2020 Dissertation Committee, Rebecca Rothberg, *Harm Reduction and Addiction Treatment*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2020 Dissertation Chair and Review Committee Chair for Benjamin Greenberg, *Shared Medical Appointments for Buprenorphine Prescribing for Individuals with Opioid Use Disorder: A Qualitative Study*, PsyD Consortium, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California

2020 Master's Thesis Advisor for Enrique Cazares-Navarro, *Trends of Benzodiazepine Use in the United States Among Older Adults: Clinical visits that include a benzodiazepine (Xanax, Valium, Klonopin) prescription have persisted between 2015 and 2019 among older adults in the continental United States, despite growing evidence of benzodiazepine harms*, Community Health and Prevention, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California

**Professional Association Membership**

2011-2016 Member, Association of Medical Education and Research in Substance Abuse (AMERSA)

2011-present Member, American Society of Addiction Medicine (ASAM)

2011-present Member, California Society of Addiction Medicine (CSAM)

2019-present Member, American Psychiatric Association (APA)

2019-present Member, American College of Academic Addiction Medicine (ACAAM)

**Regional, National, and International Service**

**Professional Societies and Advisory Boards and Committees**

2012-2015 Facilitator, California Society of Addiction Medicine (CSAM) Annual Conference, San Francisco, California

2013-2014 Advisor, American Board of Addiction Medicine Practice Improvement and Performance Measures Action Group (PIPMAG)

2013-2018 Advisor, American Board of Addiction Medicine Fellowship Development Working Group

2013-2019 Board Member, Medical Education and Research Foundation (MERF) for the Treatment of Addiction

2013-2020 Member, Public Policy Committee, CSAM

2014-2020 Member, California Society of Addiction Medicine Education Committee

2014-2018 Member, California Society of Addiction Medicine Conference Planning

2015-2019 Board Member, California Society of Addiction Medicine

2015-2016 Representative, American Society of Addiction Medicine PCORI Workshop: *Long-Term Use of Opioids for Chronic Pain*

2015-2017 Representative, Appointed by Governor Jerry Brown to the Research Advisory Panel of California, January 2015

2015-2019 Member, Public Policy Committee, American Society of Addiction Medicine

- 2015-2016 Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2017 Vice-Chair, Conference Planning Committee, California Society of Addiction Medicine Annual Conference
- 2016-2020 Member, Physicians for Responsible Opioid Prescribing (PROP)
- 2016-2018 President, Addiction Medicine Fellowship Directors Association (AMFDA)
- 2019 Advisor, Task force for The Center on Addiction (a merger between Partnership for Drug Free Kids and CASA Columbia)
- 2019-2023 Board Member, American College of Academic Addiction Medicine
- 2020-2023 Member, American College of Academic Addiction Medicine (ACAAM) Lifelong Learning and Self-Assessment Committee
- 2021-present Member, Opioid Industry Documents Archive National Advisory Committee (NAC)
- 2023-2024 Member, Recovery Expert Advisory Panel (REAP) on behalf of the Ministry of Mental Health and Addiction, Alberta, Canada
- 2022-2023 Member, Advisory Council, National Fentanyl Awareness Day
- 2023-present Board Member, State of the Nation Project

#### **Editorial Work**

- 2003-2004 Guest Editor, *Academic Psychiatry*, Issue on Women in Academia
- 2013-2014 Reviewer, *How to Find Quality Addiction Treatment*, CASA Columbia
- 2014-2017 Associate Editor, *Addiction Science and Clinical Practice (ASCP)*

#### **Ad-Hoc Manuscript/Report Review**

*Academic Psychiatry*  
*Addiction*  
*Addiction Science and Clinical Practice*  
*Agency for Healthcare Research and Quality (AHRQ)*  
*American Journal of Psychiatry*  
*Annals of Internal Medicine*

*Archives of General Psychiatry*  
*Asian Journal of Psychiatry*  
*Biological Psychiatry*  
*Bipolar Disorder*  
*British Medical Journal*  
*Cambridge University Press*  
*Culture, Medicine, and Psychiatry*  
*Current Biomarker Findings*  
*Drugs: Education, Prevention & Policy*  
*Expert Opinion on Pharmacotherapy*  
*Expert Review of Neurotherapeutics*  
*General Hospital Psychiatry*  
*Healthcare: The Journal of Delivery Science and Innovation*  
*Johns Hopkins University Press*  
*Journal of Addiction Science and Clinical Practice*  
*Journal of Affective Disorders*  
*Journal of the American Medical Association*  
*Journal of Psychiatric Research*  
*Journal of Studies on Alcohol and Drugs*  
*Medical Journal of Australia*  
*New England Journal of Medicine*  
*New Recovery Community Institutions*  
*Pain Medicine*  
*Psychological Medicine*  
*Rationality and Society*  
*Sociologic Forum*  
*Substance Abuse*  
*Substance Use and Misuse*

### **Current Funding**

2/23-1/24	Funder: Stanford Institute for Human Centered Artificial Intelligence 2022 Seed Grant Award, \$75,000 Title: Addicted by Design: An Investigation of How AI-fueled Digital Media Platforms Contribute to Addictive Consumption Role: Co-Principal Investigator (Co-PI: Johannes Eichstaedt)
7/20-6/25	Funder: Health Resources and Services Administration (HRSA), \$1,452,178, 0.1 Calendar Title: Addiction Medicine Fellowship Purpose: Stanford University Department of Psychiatry proposes to expand its existing Addiction Medicine Fellowship by two fellows in medically underserved communities in Santa Clara County Role: Principal Investigator/Project Director (Co-PI: Louie)
7/20-6/24	Funder: NIDA, \$1,050,000, 0.1 Calendar

Title: Western Node of NIDA Clinical Trials Network  
Purpose: Oregon Health Sciences University, Stanford University/Palo Alto VA, UC San Francisco, and the San Francisco Health Department propose to serve as a node in NIDA's national network which generates and support randomized clinical trials of drug addiction treatment.  
Role: Co-Investigator (MPI: Korthuis and Humphreys)

12/19-11/22 Funder: Stanford Center for Health Education ("SCHE")  
Title: Psychology of Addiction and Recovery  
Purpose: Stanford University Department of Psychiatry in partnership with SCHE and Getsmarter proposes to create an online professional education course on addiction medicine for learners around the world.  
Role: Academic Director

### **Previous Funding**

1/00-1/01 Funder: American Psychiatric Association and Eli Lilly Training Grant  
Title: Facial Emotion Processing in Patients with Bipolar Disorder  
Role: PI

7/01-7/02 Funder: National Institute of Mental Health Research Fellowship  
Title: Facial and Vocal Emotion Processing in Mood Disorders  
Role: PI

11/01-11/03 Funder: National Institute of Mental Health  
Title: Systematic Treatment Enhancement Program for Bipolar Disorder  
Role: Site-Investigator (PI: Sachs, Mass General)

12/08-12/10 Funder: National Institute of Mental Health  
Title: HPA Axis in Psychotic Depression, 2 RO1 MH050604-12  
Role: Co-Investigator (PI: Schatzberg)

10/09-10/14 Funder: National Institute on Drug Abuse  
Title: Extended Treatment for Smoking Cessation, R01 DA017441  
Role: Co-Investigator (PI: David)

7/11-7/14 Funder: National Institute of Health  
Title: Genetics of Symptomatology and Treatment Response in Depression  
Role: Investigator (PI: Murphy)

1/12-12/15 Funder: Michael Alan Rosen Foundation  
Title: Screening and Brief Intervention for Substance Misuse/Abuse  
Role: Co- PI (Co-PI: Humphreys)

11/13-11/14 Funder: Stanford Center at Peking University (SCP KU)

- Title: Narratives of Addiction in Contemporary China  
Role: PI
- 1/14-1/15 Funder: Peter F. McManus Charitable Trust, SPO #112718  
Title: Exploring Physician Opioid Prescribing Using a Novel Approach to Data Mining of Medical Records  
Role: PI
- 1/14-1/15 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation  
Title: 2014 Next Generation Award for Adolescent Substance Use Prevention  
Role: PI
- 11/14-11/15 Funder: Stanford Center for Continuing Medical Education (SCCME)  
Title: Prescription Drug Abuse: Compassionate Care for a Complex Problem  
Role: PI
- 1/15-1/16 Funder: American Board of Addiction Medicine/Conrad N. Hilton Foundation  
Title: 2015 Next Generation Award for Adolescent Substance Use Prevention  
Role: PI
- 7/16-7/17 Funder: Stanford Center for Continuing Medical Education (SCCME)  
Title: Tapering Patients off of Chronic Opioid Therapy  
Role: PI
- 11/2017 Funder: VA Center for Innovation to Implementation  
Title: The Hidden Role of Benzodiazepines in the Prescription Drug Epidemic  
Role: Small grant awardee
- 10/15-10/20 Funder: National Institute of Alcohol Abuse & Alcoholism  
Title: CNS Deficits: Interaction of Age & Alcoholism, R01 AA005965  
Purpose: Determine the impact of heavy, chronic alcohol use on brain structure and function, and the capacity of the brain to heal in a period of abstinence.  
Role: Co-Investigator (MPI: Pfefferbaum and Zahr)
- 7/18-7/21 Funder: Department of Governmental Relations, Stanford Hospital/Clinics  
Title: Addiction Medicine Peer Mentor Program  
Purpose: To explore the feasibility and safety of integrating a peer mentor into the Addiction Medicine Dual Diagnosis Clinic Treatment Team  
Role: Co-Investigator (MPI: Raheemullah and Gallagher)



## **Scholarly Work**

### **Books**

**Lembke, A.** *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Johns Hopkins University Press, November 15, 2016 (Amazon Bestseller)

**Lembke, A.** *Dopamine Nation: Finding Balance in the Age of Indulgence*, Dutton Penguin Random House, August 21, 2021 (*New York Times* Bestseller, *Los Angeles Times* Bestseller, *Washington Post* Bestseller, Audibles Bestseller, Amazon Bestseller, translated into 30 languages)

### **Peer-Reviewed Online Stanford EdX CME Courses**

**Lembke, A.** *Prescription Drug Misuse and Addiction: Compassionate Care for a Complex Problem*, produced by the Stanford Center for Continuing Medical Education, <https://www.edx.org/course/prescription-drug-misuse-and-addiction-compassionate-care-for-a-complex-problem?index=undefined>

**Lembke, A.** *Tapering Patients Off of Chronic Opioid Therapy*, produced by the Stanford Center for Continuing Medical Education, <https://www.edx.org/bio/anna-lembke>  
<https://stanford.cloud-cme.com/course/courseoverview?P=0&EID=20909>

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<https://www.pairagraph.com/dialogue/efa31e60b1e2498588ddc10d074b494c> , 2021
18. Ballanyne, Jane C.; Butler, Judy; Coelho, Paul; Franklin, Gary M.; Fugh Berman, Adriane; Gelfand, Stephen; Johnson, Chris; Juurlink, David; Kolodny, Andrew; **Lembke, Anna**; Orr, Rosemary; Streltzer, Jon; Sullivan, Mark D.; Tauben, David J. Tully, Betts; Von Korff, Michael. Letter from Physicians for Responsible

Opioid Prescribing (PROP) to the American Medical Association (AMA) -- RE: AMA's Opposition to Dose & Duration Guidance for Opioid Prescribing. <https://www.bmj.com/content/372/bmj.m4901/rr-2021>

19. **Lembke, A.**, Digital Addictions Are Drowning Us in Dopamine, *The Wall Street Journal*, August 13, 2021 <https://www.wsj.com/articles/digital-addictions-are-drowning-us-in-dopamine-11628861572>
20. **Lembke, A.** Can Bay Area entrepreneurs provide a tech solution to video game addiction? *San Francisco Examiner*, September 3, 2021 <https://www.sfexaminer.com/news/can-bay-area-entrepreneurs-provide-a-tech-solution-to-video-game-addiction/>
21. **Lembke, A.** Californians don't need another addiction crisis. Reject Prop. 27: Permitting online sports betting would increase access to a behavior that wreaks havoc on vulnerable individuals. *The San Jose Mercury News*, October 11, 2022. <https://www.mercurynews.com/2022/10/11/opinion-californians-dont-need-another-addiction-crisis-reject-prop-27/>
22. **Lembke, A.** Too much pleasure causes pain. *Institute of Art and Ideas News*, March 20, 2023, [https://iai.tv/articles/too-much-pleasure-causes-pain-anna-lembke-auid-2421?\\_auid=2020](https://iai.tv/articles/too-much-pleasure-causes-pain-anna-lembke-auid-2421?_auid=2020)
23. **Lembke, A.** Guest Editorial: History Repeats Itself: Psychedelics Are Promoted Today the Way Opioids Were Promoted in the Early 2000s. *The ASAM Weekly*, January 22, 2024. <https://www.asam.org/publications-resources/the-asam-weekly/detail/2024/01/22/guest-editorial--history-repeats-itself-psychedelics-are-promoted-today-the-way-opioids-were-promoted-in-the-early-2000s>

#### **National and International Government Testimony**

1. Apr 2015 Invited expert testimony for the Congress of the United States, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations hearing entitled "Combatting the Opioid Abuse Epidemic: Professional and Academic Perspectives," Washington, D.C. <https://democrats-energycommerce.house.gov/committee-activity/hearings/hearing-on-combatting-the-opioid-abuse-epidemic-professional-and>
2. Sep 2015 Invited expert testimony for the White House Symposium, "Medicine Responds to the Need for Addiction Expertise", The Office of National Drug Control Policy, The White House, Washington, D.C. <https://obamawhitehouse.archives.gov/the-press-office/2015/09/18/white-house-drug-policy-office-hosts-%E2%80%9Cmedicine-responds-addiction%E2%80%9D>
3. Sep 2016 Invited expert testimony for the United States Senate, Committee of Homeland Security and Government Affairs, Permanent Subcommittee on

Investigations, on the overuse and overprescribing of prescription opioids, “Combating the Opioid Epidemic: A Review of Anti-Abuse Efforts by Federal Authorities and Private Insurers”, Washington, D.C.

4. Oct 2016 Invited expert testimony for the White House Symposium, “Academic Medical Centers as Centers of Excellence in Addiction Medicine”, The Office of National Drug Control Policy, The White House, Washington, D.C.  
<http://www.abms.org/news-events/white-house-symposium-briefing-session-on-addiction/>
5. May 2017 Invited expert consultation on curbing the opioid epidemic to Nevada’s Office of the Governor
6. May 2017 Invited expert consultation on curbing the opioid epidemic to Kentucky’s Office of the Governor
7. Sep 2017 Invited expert testimony for the Congress of the United States, House of Representatives, “Addiction Medicine: The Urgent Need for Trained Physicians”, hosted by The Addiction Medicine Foundation and co-sponsored by the Congressional Prescription Drug Abuse Caucus, the Congressional Addiction Treatment and Recovery Caucus, and the Congressional Bipartisan Heroin Task Force <https://www.youtube.com/watch?v=y6kBoQckmHw>
8. Jan 2018 Invited expert testimony in federal court, Judge Dan Polster presiding, in the multi-district litigation lawsuit against opioid manufacturers and distributors <https://www.law360.com/articles/1008010/inside-the-opioid-mdl-s-big-closed-door-hearing>
9. Mar 20, 2019 Invited expert testimony for the Joint Hearing of Senate and General Assembly Health and Human Services Committees on “Opioids, cannabis, and vaping: Using science to protect public health,” State of Rhode Island
10. Jan 18, 2022, Invited expert testimony for the Kentucky circuit court judges on the role of the opioid industry in promoting misleading messages about opioids. This presentation was given at the invitation of the “Science and the Law” initiative at the American Association for the Advancement of Science (AAAS), the largest multidisciplinary scientific society in the world, and a 501(c)(3) non-governmental organization, in conjunction with the Administrative Office of Kentucky Courts.
11. February 2022, Invited expert testimony for elected representatives in Edmonton, Canada at the invitation of the Ministerial Assistant to the Associate-Minister of Mental Health and Addictions on curbing the opioid epidemic.
12. February 2022, Invited expert testimony for U.S. Senate Judiciary Committee, Hearing Examining Kids’ Online Safety

13. March 2023 Testimony for Commerce Finance and Policy Committee, the Minnesota House of Representatives and the Minnesota State Senate Examining Kids' Online Safety

**Medical Expert Witness (last 5 years)**

1. People v. Philip Morris Ingram, (Cal. Super. Ct., Docket 62-144622)
2. National Prescription Opiate Litigation, MDL No. 2804 (N.D. Ohio, Case 1:17-md-2804)
3. In Re Opioid Litigation, (Suffolk County, New York Supreme Court, Index No. 400000/2017), relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018
4. Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation, No. 1:17-op-45053-DAP and No. 1:17-op-45054
5. People of the State of California v. Purdue Pharma, L.P., et al., No. 30-2014-00725287-CU-BT-CXC
6. Miner v. Olsen, et al. (arbitration)
7. The County of Lake, Ohio v. CVS Health Corporation., et al, No. 18-op-45032 and 18-op-45079
8. The City and County of San Francisco, et al., vs. Purdue Pharma L.P., et al., No. 18-cv-07591-CRB

**Selected Invited Lectures, Domestic and International (2015-present)**

1. Feb 2015 *Drug Addiction and the Internet: Justin's Story*, Psychiatry Grand Rounds, Alta Bates Summit Medical Center, Berkeley, California
2. Feb 2015 *Pain, Addiction, and the Drug-Seeking Patient: Compassionate Care for a Complex Problem*, Santa Clara Valley Medical Center CME Symposium on Addiction, Santa Clara, California
3. Mar 2015 *The Prescription Drug Epidemic: Technology as Both Friend and Foe*, Northern California Psychiatric Society Annual CME Conference, Monterey, California
4. Sept 2015 *The Prescription Drug Epidemic: Preserving Compassion for the Drug-*



*Seeking Patient*, Mills Peninsula Health Services CME Lecture Series, San Mateo, California

5. Sept 2015 *The Prescription Drug Epidemic: Compassionate Care for a Complex Problem*, Psychiatry Grand Rounds Speaker, Oregon Health Sciences University, Portland, Oregon
6. Oct 2015 *Chronic Pain and Addiction: The Compassionate Doctor, The Narcissistic Injury, and the Primitive Defense*, California Society of Addiction Medicine, State of the Art Annual Conference, San Francisco, California
7. Oct 2015 *Prescription Drug Misuse and the Doctor Patient Relationship*, Keynote Speaker, American Correctional Healthcare Services Association, Tailoring Health Care for Inmates, Sacramento, California
8. Oct 2015 *Addiction Medicine: Managing Prescription Drug Misuse and Addiction*, Emerging and Innovative Trends in Psychiatry and Behavioral Health, Stanford University School of Medicine, Stanford, California
9. Oct 2015 *The Prescription Drug Epidemic: How Doctors are Complicit, and How We Can Do Better*, Regional Medical Center of San Jose CME Lecture Series, San Jose, California
10. Dec 2015 *Exploring Dual Diagnosis: What came first, the substance use disorder or the psychiatric disorder, and does it even matter?* Mills Peninsula Health Services CME Lecture Series, San Mateo, California
11. Jan 2016 *The Prescription Drug Epidemic and the Doctor Patient Relationship*, San Francisco General Hospital Primary Care Grand Rounds, San Francisco, California
12. Mar 2016 *Protecting our Developing Youth: Adolescent Addiction, Prevention and Recovery*, Keynote Speaker, Adolescent Counseling Services, East Palo Alto, California
13. Mar 2016 *Opioid Therapy for Chronic Non-Cancer Pain*, 2016 Third Annual Addiction Medicine Conference, San Jose Valley Medical Center, San Jose, California
14. Mar 2016 *The Prescription Drug Epidemic*, Keynote Speaker, Stanford Annual Adjunct Faculty Retreat, Palo Alto, California
15. Mar 2016 *Chronic Opioids: Shifting the Paradigm*, Keynote Speaker, Samaritan Center & Health Career and Training Center, Lebanon, Oregon
16. Jun 2016 *The Compassionate Doctor, the Drug Seeking Patient, the Narcissistic Injury, and the Primitive Defense*, Keynote Speaker, Cedar Sinai Annual Psychiatric

Conference, Los Angeles, California

17. Sep 2016 *Myths and Facts about Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC
18. Sep 2016 *Getting Patients Off of Opioids*, DCRx: The DC Center for Rational Prescribing; <http://doh.dc.gov/dcrx>, Washington, DC
19. Sep 2016 *Pharmacotherapy for Substance Use Disorders*, Department of Psychiatry Annual CME Conference, Stanford University School of Medicine, Stanford, California
20. Oct 2016 *State of the Art Treatment for Substance Use Disorders and other Addictions*, Keynote Speaker, 3-part lecture series, Beijing University, #6 Hospital, Beijing, China
21. Nov 2016 *Prescription Drug Misuse and the Doctor Patient Relationship*, Psychiatry, San Mateo County Health Systems Grand Rounds, San Mateo, California
22. Jan 2017 *Effective Strategies for the Non-Adherent Buprenorphine Patient: Rational Monitoring and Contingency*, California Society of Addiction Medicine, Treating Addiction in the Primary Care Safety Net, Webinar
23. Feb 2017 *How to safely taper patients off high dose prescription opioids for chronic pain*, Keynote Speaker, California Center for Care Innovations, Treating Addiction in the Primary Care Safety Net, Los Angeles, California
24. Feb 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Parents Weekend Back to School, Stanford, California
25. Feb 2017 *When Pain Treatment Becomes Addiction Treatment*, American Psychological Association Annual Meeting, San Francisco, California
26. Feb 2017 *Parallel Crises: The Over and Under Prescription of Opioids*, American Association of Medical Colleges (AAMC) Webinar
27. Mar 2017 *How Doctors Contributed to the Opioid Epidemic, and What We Can Do to Fix It*, Intermountain Health Care Book Club Speaker for *Drug Dealer, MD*, Intermountain Health Care, Salt Lake City, Utah
28. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Culture and Politics of Mental Health, Anthropology 1737-1020, Professor Tomas Matza, University of Pittsburg, Pittsburg, Pennsylvania
29. Mar 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Santa Cruz Health Care Initiative, Santa Cruz, California

30. Mar 2017 *The Canary in the Coal Mine: The Prescription Drug Epidemic as a Symptom of a Faltering Health Care System* Valley Care Medical, Pleasanton, California
31. Mar 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Northern California Psychiatric Society, Napa Valley, California
32. Apr 2017 *Pharmacotherapy for Addictive Disorders*, Alta Bates Grand Rounds, Alta Bates Hospital Berkeley, California
33. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Stanford TEDx, Stanford, California
34. Apr 2017 Invited speaker, 6th Annual *Health Technology Forum Innovation Conference: Common Good!* Stanford University School of Medicine, Stanford, California
35. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, 8th Annual Lloyd C. Elam Symposium, Meharry Medical College, Nashville, Tennessee
36. Apr 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, Association of Contextual Behavioral Sciences (ACBS), Chicago, Illinois
37. May 2017 *The Worst Opioid Epidemic in U.S. History: How did we get here, and how can we get out?* Stanford Health Matters, Stanford, California
38. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Central California Alliance for Health (the Alliance), Merced, California
39. May 2017 *The Compassionate Doctor, the Suffering Patient, and the Prescription Drug Epidemic*, Janus of Santa Cruz, Seaside, California
40. May 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, OPG 6th Annual Pain Conference Agenda, Ashland, Oregon
41. May 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Internal Medicine Residency Program Invited Visiting Professor and Grand Rounds Speaker, Johns Hopkins Bayview Medical Center, Baltimore, Maryland

42. Jun 2017 *Invisible Forces Driving the Opioid Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, PharmedOut Annual Conference, Georgetown University Medical Center, Washington, DC
43. Jun 2017 *Overprescribing in the Elderly: Causes, Risks, and Interventions*, Keynote Speaker at the 17th Annual California Senior Injury Prevention Educational Forum, Oakland, California
44. Sep 2017 *The Opioid Epidemic*, Keynote Speaker, Department of Labor West Coast Symposium, San Francisco, California
45. Sep 2017 *Treating Addiction without Feeding It*, Keynote Speaker, American Correctional Health Services Association (ACHSA) "Modern Challenges in Jails and Prisons", San Jose, California
46. Sep 2017 *Invisible Forces Driving the Prescription Drug Epidemic: From Disability Reform to Illness Narratives*, Keynote Speaker, The International Benzodiazepine Symposium, Redmond, Oregon
47. Sep 2017 *Reframing Medical Practice Involving Controlled Substances*, Keynote Speaker, The Association of State and Territorial Health Officials (ASTHO) 2017 Annual Conference, Washington, DC
48. Oct 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Keynote Speaker, The Patient Safety Institute for Mission Health 3rd Annual National Patient Safety Conference – Cultivating a Culture of Safety, Asheville, North Carolina
49. Nov 2017 *The Opioid Epidemic, How We Got Here, and How We Can Get Out*, Keynote Speaker, American Association of Medical Colleges, Learn, Serve, Lead, Boston, Massachusetts
50. Nov 2017 *The Opioid Fallout: Lives, Jobs and a Lost Generation*, Bloomberg News Live, The Year Ahead, Bloomberg Headquarters, New York City, New York
51. Nov 2017 *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*, Grand Rounds Speaker, Westchester Medical Center, Westchester, New York
52. Dec 2017 *The Opioid Epidemic: How We Got Here, and How We Can Get Out*, Keynote Speaker, Primary Care and Behavioral Health Integration Summit, Health Quality Partners, San Diego, California
53. Jan 2018 *How to Survive in a Dopamine Saturated World*, Psychiatry Grand Rounds, Vanderbilt University School of Medicine, Nashville, Tennessee

54. Feb 2018 *Is Marijuana a Harm Reduction Strategy?*, Stanford Psychiatry Grand Rounds, Stanford University School of Medicine, Stanford, California
55. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Woodside Priory High School, Woodside, California
56. Mar 2018 *Raising T(w)eens in a Dopamine Saturated World*, Sacred Heart High School, Menlo Park, California
57. Apr 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, California Pacific Medical Center Internal Medicine Grand Rounds, San Francisco, California
58. Apr 2018 *Adolescent Substance Abuse: Risk, Resilience, Prevention, and Treatment*, 2018 Adolescent Mental Wellness Conference, sponsored by Stanford University, Santa Clara, California
59. Apr 2018 *Drug Dealer, MD*, Keynote Speaker, STAR Trauma Recovery Center, Ohio State University Medical School, Columbus, Ohio
60. May 2018 *The Opioid Epidemic: What Doctors and Hospitals Can Do*, Alpha Omega Alpha Visiting Professorship, Psychiatry Grand Rounds, University of Kansas School of Medicine, Kansas City, Kansas
61. May 2018 *Opioids, Pain and Addiction Treatment: Pioneering Change*, Oregon Pain Guidance Annual Conference, Eugene, Oregon
62. Jun 2018 *The Opioid Epidemic, How We Got Here and How to Get Out*, Indiana Prosecuting Attorneys Council (IPAC), invited speaker, French Lick, Indiana
63. Jun 2018 *What is Addiction and How to Treat It*, Perrin's Opioid Litigation Conference, Dallas, Texas
64. Jul 2018 *Understanding the Opioid Crisis at the End of Life*, San Francisco Bay Area Hospice and Palliative Nurses Association, Stanford, California
65. Aug 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Apple Corporation, Cupertino, California
66. Aug 2018 Moderator, *Beyond Nature and Nurture – Social Determinants of Addiction and Health*, California Society of Addiction Medicine State of the Art Annual Conference, San Francisco, California
67. Aug 2018 *Drug Dealer, MD: The Opioid Crisis*, Apple Corporation Wellness Outreach, Cupertino, California
68. Sep 2018 *The Opioid Epidemic: How We Got Here, and How to Get Out*, Public

Funds Forum, Laguna Beach, California

69. Sep 2018 *Drug Dealer, MD: The Opioid Crisis*, Baton Rouge Health District Community Service Talk and Medical Center Grand Rounds, Baton Rouge, Louisiana
70. Sep 2018 *Drug Dealer, MD: The Opioid Crisis*, Montrose Annual CME Conference, Montrose, Colorado
71. Oct 2018 *The Pleasure Pain Balance*, Los Altos High School “STEAM Week”, Los Altos, California
72. Oct 2018 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote Speaker, PerformRX Pharmacy Benefits Manager Annual Conference, Orlando, Florida
73. Oct 2018 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Distinguished Lecture Series, Annual Meeting of the American Academy of Psychiatry and the Law (AAPL), Austin, Texas
74. Oct 2018 *Drug Dealer MD: The Opioid Epidemic*, Keynote Speaker, Psych Congress, Orlando, Florida
75. Dec 2018 *How to Taper Patients Off of Chronic Opioid Therapy*: 69th Annual Refresher Course for Family Physicians, Montreal, Canada
76. Jan 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of a Faltering Health Care System*, Internal Medicine Grand Rounds, Santa Clara Valley Medical Center, Santa Clara, California
77. Feb 2019 *Our Other Prescription Drug Problem (Benzodiazepines and How to Taper)*, Internal Medicine Grand Rounds, San Mateo Medical Center, San Mateo, California
78. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, National Keynote Speaker, Ohio State University Inter-Professional Summit, Columbus, Ohio
79. Feb 2019 *The Opioid Epidemic: How We Got Here, Where We Are Now, and How to Get Out*, Keynote Speaker, Pain and Addiction Summit, AT&T Conference Center/University of Texas, Austin, Texas
80. Apr 2019 *The Opioid Epidemic: From Freud to Fentanyl*, Keynote, Speaker, Geminus Community Partners Annual Conference, Merrillville, Indiana
81. Apr 2019 Invited commentator on *Deaths of Despair* for honorees Princeton Economists Ann Case and Angus Deaton, The 2019 Tanner Lectures on Human Values, Sponsored by the Office of the President and the McCoy Family Center for



Ethics in Society, Stanford, California

82. Apr 2019 *The Opioid Epidemic: Where We Are Now*, Keynote speaker for the National Council on Alcoholism and Drug Abuse (NCADA) Spring Awards Luncheon, St. Louis, Missouri
83. May 2019 *The Opioid Epidemic: Where We Are Now*, Faculty presenter Stanford Sierra Camp Womens' Alumni Wellness Retreat, Fallen Leaf Lake, California
84. May 2019 *The Opioid Epidemic: From Freud to Fentanyl*, The American Psychiatric Association Annual Meeting, San Francisco, California
85. Jul 2019 *Social Media and Device Addiction*, 27th Annual Pediatric Update, Stanford University School of Medicine, Stanford, California
86. Jul 2019 *Rethinking Opioid Tapers, Buprenorphine Induction, and Perioperative Buprenorphine*, Opioid Response Network Texas Grand Rounds National Webinar Series
87. Jul 2019 *Tapering Guidance for Opioids*, National Academy of Medicine webinar <https://nam.edu/event/webinar-tapering-guidance-for-opioids-existing-best-practices-and-evidence-standards/> ; <https://nam.edu/wp-content/uploads/2019/08/Tapering-webinar-two-pager-FINAL.pdf>.
88. Aug 2019 *Medical Cannabis: Clinical Issues*, 8<sup>th</sup> Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, California
89. Nov 2019 *Tapering Opioids: Compassionate Care or Punitive Policy*, AMERSA Conference, Boston, Massachusetts
90. Dec 2019 *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Southwestern Gynecologic Assembly 54<sup>th</sup> Annual Meeting: Patient and Provider at Their Best: Caring for Patients and Yourself, Dallas, Texas
91. Mar 2020 *Dismantling the Addiction Industrial Complex*, 13th Annual Haas Healthcare Conference, "Foresight is 2020," San Francisco, California
92. Jun 2020, *From Freud to Fentanyl: The Opioid Epidemic as a Symptom of our Faltering Health Care System*, Alta Bates Grand Rounds, Berkeley, California
93. Aug 2020 *Cannabis: A Practical Clinical Approach*, 9<sup>th</sup> Annual Navigating Spine Conference, Stanford University School of Medicine, Stanford, California
94. Aug 2020 *What's Next in the Opioid Epidemic: How to Taper Long-Term Opioid Therapy*, The Align Conference Evidence in Motion, online conference



95. Oct 2020 *The Opioid Epidemic, An Update ... Plus A Word on Cannabis*, James O. Johnson Orthopedic Symposium, The Kaiser Permanente Group, online conference
96. Nov 2020 *Aging and Alcohol: How Much Is Too Much?* Avenidas Town Hall, Palo Alto, California
97. Dec 2020 *Chatham House Webinar: Freedom of Thought and Opinion in the Digital Age*, The Royal Institute of International Affairs Chatham House, 10 St James's Square, London, England
98. Dec 2020 *Benzodiazepines: A Crisis Hidden in Plain Sight*, American Academy of Addiction Psychiatry, San Antonio, Texas.
99. Jan 2021 *The Impact of Technology on Mental Health*, Q & A with Microsoft Interns, online panel discussion with Tim Kendall and Jaron Lanier
100. Jan 2021 *Addiction and Technology*, online guest speaker and panelist, University of Toronto Artificial Intelligence Conference, Toronto, California
101. Jan 2021 *Physicians with Addiction: Why it Happens and How to Help*, Department of Anesthesiology, Stanford Health Care, Kaweah Delta, California
102. Feb 2021 *The Neuroscience of Addiction*, Recovery Café, San Jose, California
103. Feb 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Luxembourg Stanford Alumni Association, Luxembourg
104. Feb 2021 *Social Media: Why It's Addictive and How to Use It in Healthier Ways*, National Association of Pediatric Nurse Practitioners, San Francisco, California
105. Mar 2021 *Social Media: Why It's Addictive and How to Use It in Healthier Ways*, The Royal Institute of International Affairs Chatham House, 10 St James's Square, London, England
106. Mar 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Alpha Omega Alpha Visiting Professorship Grand Rounds, University of Nevada Medical School (Reno)
107. Mar 2021 *The Science of Addiction: What It Is, How It Affects Our Brains, and What We Can Do About It*, Stanford University Healthy Living Class, Stanford, California
108. Mar 2021 *Alcohol Use Disorder: How Much is Too Much?* Sage Eldercare, Bay Area, California

109. Apr 2021 *Caring for Ourselves as We Care for Patients with Substance Use Disorders*, San Mateo County Health Care System Wellbeing Series, Bay Area, California
110. May 2021 *Technology: Savior or Threat: A Panel Discussion*, How the Lights Get In Festival, The Institute of Art and Ideas, London, England
111. Jun 2021 *Social Media Addiction: Why It Happens and What To Do About It*, Grand Rounds at Mercy Fitzgerald Hospital, Philadelphia
112. Oct 2021 *The Kennedy Forum: A Panel Discussion with Jonathan Haidt on the Impact of Social Media on Mental Health*
113. Oct 2021 Mental Health Alliance of San Mateo County, *Dopamine Nation: Finding Balance in the Age of Indulgence*
114. Oct 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, McCallie School, Chattanooga, Tennessee
115. Nov 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence* for Young Presidents Organization (YPO), Fort Worth, Texas
116. Nov 2021 Alta Bates Grand Rounds, *Dopamine Nation: Finding Balance in the Age of Indulgence*, Berkeley, California
117. Nov 2021 *Confronting Global Health Challenges*, *Dopamine Nation*, Duke University, Durham, North Carolina
118. Nov 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence* for Young Presidents Organization (YPO), Dallas, Texas
119. Feb 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence* for Stanford Faculty Help Series Lecture
120. Feb 2022 *Digital Addictions*, IPCAP's 20th National Convention, Philippines
121. Feb 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Eckerd College, St. Petersburg, Florida
122. Feb 2022 *Digital Addictions*, Keynote, Harvard College Project for Asian and International Relations, Boston, Massachusetts
123. Mar 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Santa Cruz County Health Services Agency
124. Mar 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence* for YPO,

Kansas City, Missouri

125. Mar 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, University of Chicago Grand Rounds, Freedman Memorial Lecture, Chicago, Illinois
126. Apr 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Grand Rounds for Rush Medical School, Chicago, Illinois
127. Apr 2022 Panelist for Stanford's Human Centered Artificial Intelligence Annual Conference, Stanford University, Stanford, California
128. April 2022 *Dopamine Nation and the Neuroscience of Addiction*, Lavin Event, Case Western Reserve University, Cleveland, Ohio
129. May 2022 *The Neuroscience of Addiction*, The WellHouse Keynote Address, Stanford University, Stanford, California
130. May 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Health Matters, Stanford University Medical School, Stanford, California
131. May 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Carle Addiction Medicine Grand Rounds, Illinois
132. May 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, National Association of Branch Campus Administrators, Stanford University, Stanford, California
133. May 2022 *Homelessness in California*, Panelist, SIEPR, Stanford University, Stanford, California
134. Jun 2022 *Logging into the Burden of Technology and Social Media on Mental Health*, University of Melbourne's student conference MDSC, Melbourne, Australia
135. Jul 2022 *Dopamine Nation : Finding Balance in the Age of Indulgence*, Lowcountry Mental Health Conference, Charleston, South Carolina
136. Aug 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, Psych Club of Manipal Academy of Higher Education, Manipal, Karnataka, India
137. Aug 2022. *Resisting Digital Temptations: How AI Fuels Addiction*, Human Artificial Intelligence Congressional Bootcamp, Stanford University, Stanford, California
138. Aug 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, UNSW Sydney during National Science Week, Sydney, Australia

139. Aug 2022 *Dopamine: A Practical Approach to Compulsive Overconsumption in a Reward-Overloaded World*, Kaiser Permanente Mental Health & Addiction Medicine Symposium, California
140. Oct 2022 *Dopamine in Conversation with Dr. Kevin McCauley*, Trauma and Addictions Conference, Las Vegas, Nevada
141. Oct 2022 *The Digital Age of Vulnerability: Better Social Media & Mental Health*, State University of New York Plattsburgh at Queensbury and State University of New York, Adirondack, Queensbury, New York
142. Oct 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, International Association of Orofacial Myology (IAOM), Kansas City, Missouri
143. Nov 2022 PCSS Clinical Roundtable - *Drs. Andrew Kolodny and Anna Lembke - Buprenorphine and Chronic Pain*
144. Nov 2022 *A Neuroscience Informed Approach to Compulsive Overconsumption*, Louisiana State University Psychiatry Grand Rounds, Baton Rouge, Louisiana
145. Nov 2022 *Dopamine Fasting: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine Overloaded World*, the Global Exchange Conference, Orlando, Florida
146. Nov 2022 *Dopamine Nation: Finding Balance in the Age of Indulgence*, NotMYkids Annual Breakfast, Scottsdale, Arizona
147. Nov 2022 *Opioids and Opioid Use Disorder*, American College of Academic Addiction Medicine Didactic Series
148. Nov 2022 *How to Talk to Teens about Addiction*, The Glenbard Parent Series, Chicago, Illinois
149. Dec 2022 *Translating Addiction Science to Practice and Policy: A Dialogue*, Department of Psychiatry Grand Rounds, Stanford University, Stanford, California
150. Dec 2022 *How to Talk to Teens about Addiction*, Parents' Coalition of Bay Area High Schools, San Francisco, California
151. Dec 2022 *How to Talk to Teens about Addiction* Palo Alto and Gunn High School Parent Series, Palo Alto, California
152. Feb 2023 *Radical Honesty: How Telling the Truth Changes our Brains and Promotes Recovery* Keynote Address, Last Door Recovery Society, Calgary, Alberta, Canada

153. Feb 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World* Keynote Address, Parker University Annual Chiropractic Conference, Las Vegas, Nevada
154. Mar 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World* Live Healthier Longer Summit, Naples, Florida
155. Mar 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Stanford Grad Alumni Day, Stanford, California
156. Mar 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, for Careers, Life, and Yale, New Haven, Connecticut
157. Apr 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Slovenia Talk Fit4Kid International Scientific Conference Keynote Address, Slovenia
158. Apr 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Stanford Continuing Studies, Stanford, California
159. Apr 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Science and Cocktails, Copenhagen, Denmark
160. Apr 2023 *Social Media and Children's Mental Health*, Panelist, Jewish Family Services and Common Sense Media, Palo Alto, California
161. Apr 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Keynote, International Institute for Trauma and Addiction Professionals, Phoenix, Arizona
162. Apr 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Keynote, Women Physicians' at Honor Health Foundation Keynote Address, Phoenix, Arizona
163. May 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, Common Ground and Sacred Heart Prep Keynote Address, Menlo Park, California
164. May 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption with a Focus on Social Media*, Dupage County Health Department, Glenellyn, Illinois

165. May 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption in a Dopamine-Overloaded World*, “Change” Psychology Conference, Milan, Italy
166. Jun 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption*, University Medical Center Grand Rounds, Chicago, Illinois
167. Jun 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption*, Reeves Warm, MD Endowed Lecturer at University Hospitals in Cleveland, Ohio
168. Jun 2023 *The Potential Harm of Social Media*, Representative DeSaulnier Town Hall, California
169. Jul 2023 *A Child’s Mind on Tech*, Center for Innovation and Resources, California
170. Jul 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption*, Ohio State Addiction Studies Institute Keynote Address
171. Jul 2023 *Dopamine Nation: A Neuroscience Informed Approach to Compulsive Overconsumption*, Parker Seminar Series “Neuron” Keynote Address, Dallas, Texas
172. Aug 2023 *Dopamine Nation*, The Institute of Art and Ideas, London, United Kingdom
173. Aug 2023 *The Plenty Paradox*, The Institute of Art and Ideas Panel on Desire, Struggle, and the Search for Wellbeing, London, United Kingdom
174. Aug 2023 *Addiction and Digital Media*, Human-Centered Artificial Intelligence Congressional Bootcamp, Stanford, California
175. Aug 2023 *The Impact that Technology, Social Media, and Digital Addiction Have on our Health and Wellbeing*, Dakota Medical Foundation Health and Wellbeing Summit Keynote Address, Fargo, North Dakota
176. Aug 2023 *Opioids and Opioid Use Disorder: A Review*, The American College of Academic Addiction Medicine (ACAAM) Didactic Lecture Series
177. Sep 2023 *Dopamine Fasting: An Early Intervention for Compulsive Overconsumption in the Digital Age*, California Society of Addiction Medicine (CSAM) Keynote Address, San Diego, California
178. Oct 2023 *Radical Honesty: How Telling the Truth Promotes Recovery*, International Conference for Secular AA Keynote Address

179. Oct 2023 *Substance Use Disorders and Mood Disorders*, 19th Annual Stanford Mood Disorders Education Day, Translating Emerging Treatments for Mood Disorders into Practice
180. Oct 2023 “*DOPAMINE*”: *A Neuroscience Informed Approach to Dopamine Fasting in the Digital Age*”, U.S. Marines Commanders Huddle, Norfolk, Virginia
181. Oct 2023 “*DOPAMINE*”: *A Neuroscience Informed Approach to Dopamine Fasting in the Digital Age*,” Lifestyle Medicine Annual Conference, Denver, Colorado
182. Nov 2023 Annual Feldman Lecturer for the 38<sup>th</sup> Feldman Lecture Series, composed of three lectures by a single scholar over the course of one day, Edmonton Canada. Feldman Lectures: 1.) The Plenty Paradox: How Abundance Has Made Us More Vulnerable to Addiction and Other Forms of Suffering; 2.) The Gap Between Evidence and Promotion: How Today’s Discourse on Cannabis and Psychedelics Echoes Two Decades of Misleading Opioid Marketing; 3.) Radical Honesty, Narcissism, and Surrender: Psychospiritual Aspects of Addiction and Recovery
183. Nov 2023 *Dopamine Nation: Finding Balance in the Age of Indulgence*, HSM+, Sao Paulo, Brazil
184. Dec 2023 *Dopamine Nation: Finding Balance in the Age of Indulgence* Genius Network, Phoenix, Arizona

**Media Appearances (2015-present)**

1. Apr 2015 *Public Radio International-To the Point*, hosted by Warren Olney, prescription opioid and heroin abuse in America, invited expert.
2. Oct 2015 *OnPoint*, *National Public Radio*, the prescription opioid epidemic, invited expert
3. Mar 2016 *Al Jazeera* live programming, the new CDC guidelines on opioid prescribing, invited expert
4. Mar 2016 *KCBS Radio*, San Francisco, the new CDC guidelines on opioid prescribing, invited expert
5. Apr 2016 *The Today Show* on NBC, NY, New York, appearance with Mehmet Oz discussing “The Opioid Epidemic”
6. May 2016 *KCBS Radio*, San Francisco, the FDA approves Probuphine, a buprenorphine implant, invited expert
7. Oct 2016 *Opioids: Last Week Tonight with John Oliver* (HBO),  
<https://www.youtube.com/watch?v=5pdPrQFjo2o>



8. Nov 2016 *Sirius XM Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
9. Nov 2016 *Wisconsin Public Radio's "Central Time" Show*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://www.wpr.org/connection-between-illicit-drugs-and-doctors>
10. Nov 2016 *The Healthcare Policy Podcast with David Introcaso*, invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://www.stitcher.com/podcast/david-introcaso-2/the-healthcare-policy-podcast/e/what-explains-the-opioid-epidemic-dr-anna-lemcke-discusses-48277528>
11. Nov 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://straighttalkmd.com/podcast/drug-dealer-md-opioid-epidemic-anna-lemcke-md/>
12. Nov 2016 *Conversation on Healthcare Reach MD Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://www.chcradio.com/episode.php?id=360>
13. Nov 2016 *KALW Local Public Radio*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://kalw.org/post/city-visions-how-doctors-fueled-opioid-epidemic#stream/0>
14. Nov 2016 *Forum with Michael Krasny (KQED-FM)* invited panelist to discuss "The Surgeon General's Report: Facing Addiction in America," <https://ww2.kqed.org/forum/2016/11/28/addiction-is-illness-not-a-moral-failing-says-surgeon-general/>
15. Nov 2016 *Stanford Scope 1:2:1 Podcast with Paul Costello* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://med.stanford.edu/news/all-news/one-to-one/2016/drug-dealer--md--how-physicians-are-fueling-the-opioid-epidemic.html>
16. Dec 2016 *Straight Talk MD with Frank Sweeny* invited podcast to discuss "The Surgeon General's Report: Facing Addiction in America," <https://www.acast.com/straighttalkmd/facing-addiction-in-america-the-surgeon-generals-report>
17. Dec 2016, *NPR Fresh Air with Terry Gross* 'Drug Dealer, M.D.': Misunderstandings And Good Intentions Fueled Opioid Epidemic invited interview to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard*

to Stop <http://www.npr.org/sections/health-shots/2016/12/15/505710073/drug-dealer-md-contends-that-well-meaning-docs-drove-the-opioid-epidemic>

18. Dec 2016 *The Jimmy Moore Show* invited podcast to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
19. Feb 2017 *WILK Radio, The Sue Henry Show* invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
20. Feb 2017 Reach, MD with host John J. Russell, MD invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <https://www.reachmd.com/programs/book-club/drug-dealer-MD-how-doctors-duped-patients-hooked-why-so-hard-stop/8512/>
21. Mar 2017 *MSNBC with Chris Hayes*, live guest appearance to discuss the opioid epidemic in West Virginia <https://www.youtube.com/watch?v=0Ar30-kDSUQ&sns=em>
22. Mar 2017 *Stanford Law School Wellness Project Podcast*, with Dr. Joseph Bankman and Dr. Sarah Weinstein, to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* [www.law.stanford.edu/wellnessproject](http://www.law.stanford.edu/wellnessproject)
23. Mar 2017 *SiriusXM's Tell Me Everything with John Fugelsang*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
24. Jun 2017 *The Texas Standard Radio Show*, invited guest to discuss the FDA decision to ask Endo Pharmaceuticals to withdraw Opana ER from the market <http://www.texasstandard.org/stories/fda-wants-painkiller-favored-by-opioid-abusers-off-the-market/>
25. Jun 2017 *NBC Television Sunday Night with Megyn Kelly*, invited expert to discuss marijuana legalization <http://www.nbc.com/sunday-night-with-megyn-kelly/video/sunday-night-with-megyn-kelly/3536915>
26. Jun 2017 *KCBS Radio in San Francisco* invited guest to discuss the ongoing opioid epidemic
27. Jul 2017 *KPCC's AirTalk* with host Larry Mantle, live guest appearance to discuss the opioid crisis <http://www.scpr.org/programs/airtalk/2017/07/20/58084/in-the-context-of-the-opioid-crisis-doctors-discus/>
28. Jul 2017 *Jose Calderon Mindful Psychiatry Live Radio and Podcast*, invited guest to discuss *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop* <http://wholebodymentalhealth.libsyn.com/hard-pill-to->

swallow-drug-dealer-md-with-dr-anna-lempke-md-7-5-17

29. Aug 2017 KQED Forum with Michael Krasny Live Radio Broadcast, invited guest to discuss *Rise in High-Risk Drinking a Public Health Crisis, New Study Finds*
30. Aug 2017 MSNBC with Chris Hayes, live guest appearance to discuss President Trumps inaction on the opioid epidemic <http://www.msnbc.com/all-in/watch/donald-trump-has-done-nothing-on-the-opioid-crisis-1032009795986>
31. Sep 2017 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss CVS Pharmacy's announcement it will limit opioid prescriptions to seven days for certain conditions for new patients seeking drugs for pain relief.  
<http://www.scpr.org/programs/airtalk/2017/09/22/59288/how-much-would-cvs-s-7-day-limit-on-painkiller-pre/>
32. Oct 2017 BBC Newshour on BBC World Service radio on the opioid epidemic with host James Menendez <http://www.bbc.co.uk/programmes/w172vghc8jkr3g>
33. Oct 2017 NBCUniversal live in the studio with Dr. John Torres, One Nation Overdosed: Doctors Speak Out <http://qlnk.io/ql/59f0f15be4b0945e5d8ff73f>
34. Oct 2017 KPIX 5 CBS San Francisco Trump declares the opioid epidemic a public health emergency <http://sanfrancisco.cbslocal.com/video/3752604-critics-say-trumps-opioid-announcement-doesnt-go-far-enough/>
35. Oct 2017 KPIX 5 CBS San Francisco commentator on bay area parents using marijuana <http://sanfrancisco.cbslocal.com/2017/11/04/marin-mom-marijuana-makes-her-better-parent/>
36. Jan 2018 KQED with Brian Watt on "smartphone addiction"  
<https://soundcloud.com/kqed/investors-urge-apple-to-take-action-to-curb-digital-device-overuse-among-children>
37. Feb 2018 Sirius/XM radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on the opioid epidemic and *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*
38. Feb 2018 KQED News radio, report on Purdue Pharma's decision to stop marketing opioids directly to doctors
39. Feb 2018 NPR Smartphone Detox, How to Power Down in a Wired World  
<https://www.npr.org/sections/health-shots/2018/02/12/584389201/smartphone-detox-how-to-power-down-in-a-wired-world>
40. Mar 2018 Sirius/XM Radio with Clare Marie Gauthier, Co-Host, Dave Nemo Weekends, RadioNemo of North America, on addiction treatment

41. Mar 2018 Sirius/XM Radio “Doctor Radio”, on the silent benzodiazepine epidemic
42. Mar 2018 Sirius XM Radio: POTUS Channel 124, "Steele & Ungar", on new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
43. Mar 2018 KPCC's AirTalk with host Larry Mantle, live guest appearance to discuss new Center for Medicare and Medicaid Services regulations to restrict opioid prescribing
44. Mar 2018 Science VS. with Rose Rimler, “Opioids: Kicking America’s Addiction” <https://www.gimletmedia.com/science-vs/opioids-kicking-americas-addiction#episode-player>
45. Apr 2018 KQED Forum with Michael Krasny, Medical Community Divided On Medicare's Policy to Shorten High-Dose Opioid Prescriptions, <https://www.kqed.org/forum/2010101864587/medical-community-divided-on-medicare-policy-to-shorten-high-dose-opioid-prescriptions>
46. May 2018 Radio Health Journal with Reed Pence: The Opioid Epidemic, [http://mediatracks.com/shows/RHJ\\_18-17.mp3](http://mediatracks.com/shows/RHJ_18-17.mp3)
47. May 2018 Straight Talk MD: Health | Medicine | Healthcare Policy | Health Education | Anesthesiology, The Cannabis Conversations: Part II with Anna Lembke MD <http://straighttalkmd.com/podcast/the-cannabis-conversations-part-ii-with-anna-lembke-md/>
48. Jun 2018 The Future of Everything with Russ Altman (Stanford Radio), 06/18/18. In a recent segment on Stanford Radio, Russ Altman discussed the rise of the opioid epidemic in the United States with Anna Lembke. <https://soundcloud.com/user-458541487/facing-addiction-with-guest-anna-lembke>
49. Jul 2018 NBC News with Dr. John Torres to discuss benzodiazepines [https://www.nbcnews.com/nightly-news/video/is-anti-anxiety-medication-the-next-u-s-drug-crisis-1287215683720?cid=eml\\_onsite](https://www.nbcnews.com/nightly-news/video/is-anti-anxiety-medication-the-next-u-s-drug-crisis-1287215683720?cid=eml_onsite)
50. Oct 2018 NOVA/PBS documentary ADDICTION, Produced, Directed and Written by Sarah Holt, Co-producer Julie Crawford <http://www.holtproductions.org>; <http://www.pbs.org/wgbh/nova/body/addiction.html>
51. Mar 11, 2019 Spectrum News In Focus, What’s Causing the Opioid Crisis, with Renee Eng, <https://spectruminfocus.com/section/in-focus/in-focus/2019/03/11/in-focus--what-s-causing-the-opioid-crisis#>
52. Apr 29, 2019 KALW City Visions, California’s drug rehabilitation industry, <https://www.kalw.org/post/city-visions-reforming-californias-drug-rehabilitation->

industry#stream/0

53. May 20, 2019 Groundless Ground podcast with Lisa Dale Miller, Chronic Pain, Dual-Diagnosis and Addiction Treatment, <https://groundlessground.com/episodes/anna-lembke-chronic-pain-dual-diagnosis-and-addiction-treatment>
54. Jun 24, 2019 KCBS News Radio San Francisco 10 Q's w/Stan & Susan, to discuss rising rates of fentanyl overdose in San Francisco <https://kcbsradio.radio.com/blogs/margie-shafer/fentanyl-becomes-san-francis>
55. Jul 18, 2019 Russian Television News (RT International) "The Opioid Epidemic in the United States: Where Are We Now?" <https://www.youtube.com/watch?v=KP-Vn2d6LWk>
56. Aug 26, 2019 Russian Television News (RT International) on the Oklahoma vs Johnson & Johnson opioid litigation <https://youtu.be/sNKrMYIrPtE>
57. Aug 29, 2019 Monocle 24 Radio in London on the opioid crisis in follow up to the outcome of the Oklahoma vs Johnson & Johnson opioid litigation
58. Sep 2019 American Journal of Psychiatry Residents' Journal podcast series <http://ajpresidentsjournal.apapublishing.libsynpro.com>
59. Sep 2019 *The Voice of Medicine* podcast, [m.hulik@radiolutions.com](mailto:m.hulik@radiolutions.com)
60. Oct 2019 *This is Life with Lisa Ling*, Benzodiazepines, <https://www.cnn.com/2019/10/04/health/benzodiazepines-this-is-life-with-lisa-ling/index.html> ; <https://itunes.apple.com/us/tv-season/this-is-life-with-lisa-ling-season-6/id1480545936>
61. Oct 2019 *Straight Talk with Frank Sweeny*, Benzodiazepines, <https://podcasts.apple.com/us/podcast/straight-talk-md-health-medicine-healthcare-policy/id1060256849#episodeGuid=78d97afe7ea14dac8261193a2aa3d69> ; <https://open.spotify.com/episode/1jrtfq60dmraRnzTtsUNeb?si=jO2RZqjDTM-c1VJUVsWcuw>
62. Dec 2019 CBSN Bay Area, 12/09/19 *Medical Monday: How to avoid overindulging in alcohol during the holiday season and setting healthy drinking limits* <https://sanfrancisco.cbslocal.com/live/cbsn-bay-area/video/3439448-20191209162159-medical-mondays-dr-anna-lembke-addiction-recovery-relapse-triggers/>
63. Feb 2020 Netflix's "The Pharmacist" explores how pill mill doctors fanned the flames of the country's opioid epidemic by flagrantly overprescribing three particular drugs. Anna Lembke, associate professor of psychiatry and behavioral sciences, is

quoted in this piece. <https://www.oxygen.com/true-crime-buzz/oxycontin-soma-xanax-the-holy-trinity-from-the-pharmacist-explained>

64. Feb 2020 Anna Lembke appeared on the Netflix documentary series *The Pharmacist*. <https://www.netflix.com/title/81002576>
65. Feb 2020 *What Makes Up Your Mind: Opioids and Addiction with Dr. Anna Lembke*, Stanford University Department of Psychiatry Podcast, <https://m.soundcloud.com/stanfordpsy/february2020/s-kBmxv>
66. Feb 2020 Sirius XM Doctor Radio, invited guest to discuss benzodiazepines, Scott.Uhing@SiriusXM.com
67. Apr 2020 *Mental Health During Quarantine*, Doc to Doc with Dr. John Torres, Medical Correspondent NBC News and MSNBC, Facebook Live, <https://www.facebook.com/NBCNews/videos/doc-to-doc-coronavirus-conversation-with-dr-anna-lembke/280171329668121/>
68. Jul 2020 *The Therapy Show* with Dr. Bridget Nash, <https://www.therapyshow.com/podcasts/episode/2986f561/drug-dealer-md-author-dr-anna-lembke-discusses-the-latest-treatments>
69. Aug 2020 *How is the Pandemic Affecting People Struggling with Addiction*, Stanford Medicine Scope Interview with Paul Costello <https://scopeblog.stanford.edu/2020/08/11/how-the-pandemic-is-affecting-people-struggling-with-addiction/>
70. Aug 2020 *How the Pandemic is Affecting People Struggling with Addiction*, Stanford Medicine's Paul Costello speaks with Anna Lembke, MD, Associate Professor of psychiatry and behavioral sciences, for a 1:2:1 podcast about the impact of the pandemic on people with drug and alcohol addiction. <https://scopeblog.stanford.edu/2020/08/11/how-the-pandemic-is-affecting-people-struggling-with-addiction/>
71. Sep 2020 *COVID-19 and Mental Health with Anna Lembke MD* from Straight Talk MD with Frank Sweeny on Apple Podcasts <https://podcasts.apple.com/us/podcast/straight-talk-md/id1060256849?i=1000489628559>
72. Sep 2020 Anna Lembke appeared on the Netflix documentary *The Social Dilemma*, explaining that "social media is a drug" which exploits the brain's evolutionary need for interpersonal connection. <https://www.thesocialdilemma.com/reclaim-your-screen-time/>
73. Sep 2020 *Officers, tow truck driver released from hospital after Fentanyl exposure scare on Golden Gate Bridge*. Dr. Anna Lembke was interviewed regarding fentanyl



exposure.

<https://abc7news.com/chp-golden-gate-officers-fentanyl-exposure-bridge-crash-sf-car-crash/6421359/>

74. Oct 2020 *Anna Lembke – Episode 55*, Rallen’s Rant <https://soundcloud.com/richie-allen-3/anna-lembke-episode-55>
75. Nov 2020 *Our Social Dilemma: My Conversation with Dr. Anna Lembke* from 20 Minutes with Bronwyn <https://podcasts.podinstall.com/twentyminuteswithbronwyn-20-minutes-bronwyn/202011031100-our-social-dilemma-my-conversation-dr-anna-lembke.html>
76. Nov 2020 *The Social Dilemma of a Nation Addicted to Dopamine (ft. Dr. Anna Lembke)* from Designed to Heal. <https://podcasts.apple.com/us/podcast/designed-to-heal/id1479146995>
77. Dec 2020 *Dr Anna Lembke - Addiction and Social Media*, Woven Experiences by Marissa Monnig <https://anchor.fm/marissa-monnig/episodes/Dr-Anna-Lembke---Addiction-and-Social-Media-en7kma>
78. Jan 2021 *The Social Dilemma: Preconceived with Zale Mednick* (Apple Podcasts) <https://link.chtbl.com/FYGb94jM>
79. Jan 2021 *PharmedOut at Georgetown University Panel Discussion w/ Dr. Anna Lembke* <https://www.youtube.com/watch?v=iCaF2JSVhdg&t=6s>
80. Feb 2021 The “Addict” in All of Us: The Surprising Places Where Addiction Exists, Dr. Anna Lembke, MD, The Bottom Line Advocate With Sarah Hiner <https://bottomlineinc.com/health/addiction/the-addict-in-all-of-us-the-surprising-places-where-addiction-exists-sarah-hiner-talks-to-addiction-specialist-anna-lembke-md>
81. Feb 2021 Anna Lembke appeared on the HBO Panel regarding the documentary *The Crime of the Century* on the opioid crisis
82. Mar 2021 National Society of High School Scholars Panel with Jeff Orlowski and Tim Kendall on *The Social Dilemma* <https://www.nshss.org/events/past-webinars/>
83. Mar 2021 *Insight on the Opioid Crisis: An Interview with Dr. Anna Lembke*, The Power of the Patient Project <https://www.youtube.com/watch?v=TtMv6yNI4Uo&t=60s>
84. Mar 2021 *Dopamine Nation: Finding Balance in the Age of Indulgence*, The Parent Venture (Parent Education), Menlo Park, CA [https://www.youtube.com/watch?v=rHI4N\\_lShJI&t=14s](https://www.youtube.com/watch?v=rHI4N_lShJI&t=14s)



85. Apr 2021 Anna Lembke appeared on the HBO documentary *The Crime of the Century* on the opioid crisis  
<https://www.youtube.com/watch?v=nK1avWWjiZ4&t=76s>
86. Apr 2021 *Dopamine Nation: Social Media, Persuasion, and the Science of Addiction*, Anna Lembke in conversation with Aza Raskin, Aspen Brain Institute Expert Series <https://www.youtube.com/watch?v=T4yMzP5oCDA>
87. May 2021 *Recovery: The Hero's Journey (The Epidemic of Overprescribing Opioids and Benzodiazepines)* Interviewed by Dr. Patricia Harrigan on Mental Health for The Voice of America <https://www.voiceamerica.com/episode/131102/the-epidemic-of-overprescribing-opioids-and-benzodiazepines>
88. Jul 2021, Best Practices for Opioid Tapering, Compass Opioid Steward Program, <https://directory.libsyn.com/episode/index/id/19758497>
89. Aug 2021 Interview with Dr. David Perlmutter, MD Empowering Neurologist Podcast, about my book *Dopamine Nation*
90. Aug 2021 Interview with Terri Gross, NPR's *Fresh Air*, about my book *Dopamine Nation*
91. Aug 2021 Interview with Tucker Carlson, *The Tucker Carlson Show* FOX News, about my book *Dopamine Nation*
92. Aug 2021 Interview with Rich Roll, *The Rich Roll Podcast*, about my book *Dopamine Nation* <https://www.richroll.com/podcast/anna-lembke-623/>
93. Aug 2021 *KALW Radio*, Interview on The State of the Bay, about my book *Dopamine Nation* <https://www.kalw.org/show/state-of-the-bay/2021-08-29/the-neuroscience-of-addiction-san-franciscos-corruption-sfjazz-high-school-all-stars>
94. Aug 2021 *Laurie Interviews Dr. Anna Lembke about Addictions & How We All Have Them*, The Laurie DeYoung Show, <https://wpoc.iheart.com/featured/the-laurie-deyoung-show/content/2021-08-26-laurie-interviews-dr-anna-lembke-about-addictions-how-we-all-have-them/>
95. Aug 2021 *Is Instagram a Drug?: Dr. Anna Lembke*, SuperAge: Live Better podcast <https://podcasts.apple.com/tn/podcast/is-instagram-a-drug-dr-anna-lembke/id1514482663?i=1000533053656>
96. Aug 2021 *Dr. Anna Lembke Understanding & Treating Addiction, Episode 33*, Huberman Lab podcast, <https://hubermanlab.libsyn.com/dr-anna-lembke-understanding-treating-addiction-episode-33>
97. Aug 2021 *On the Podcast: Leigh Montville, Robert Meyer and Dan Koeppeel, and*

*Anna Lembke, This is the Author*

<https://www.penguinrandomhouseaudio.com/blog/on-the-podcast-leigh-montville-robert-meyer-and-dan-koeppeel-and-anna-lembke/>

98. Aug 2021 *Tech, Social Media & Addiction – Anna Lembke*, Engineer-Mind podcast  
<https://www.youtube.com/watch?v=qIEFb0spXRY>
99. Aug 2021 *Anna Lembke: Dopamine & Digital Addiction*, Singularity Radio  
<https://anchor.fm/singularity-radio/episodes/FBL24---Anna-Lembke-Dopamine--Digital-Addiction-e16eso2>
100. Aug 2021 *Overcoming Social Media Addiction*, Mind Espresso with Scott Engler  
<https://podcasts.apple.com/us/podcast/overcoming-social-media-addiction/id1460146095?i=1000533877661>
101. Aug 2021 *Dr. Anna Lembke: Finding Balance in a Dopamine-Overloaded World*, The Courageously. U Podcast <https://courageouslyu.com/anna-lembke/>
102. Aug 2021 *Dopamine Nation with Anna Lembke MD*, Straight Talk MD with Frank Sweeny <https://straighttalkmd.com/podcast/dopamine-nation-with-anna-lembke-md/>
103. Aug 2021 *Anna Lembke MD: social media is a drug*, Northstar Unplugged,  
<https://www.northstarsleepschool.com/anna-lembke-md>
104. Aug 2021 *Finding Balance in the Age of Indulgence: With Guest Dr. Anna Lembke*, The Rick Ungar Show <https://www.rickungarshow.com/finding-balance-in-the-age-of-indulgence-with-guest-dr-anna-lembke/>
105. Sep 2021 Interview with Joe Rogan, *The Joe Rogan Experience*, about my book *Dopamine Nation*
106. Sep 2021 *The Correlation Between the Opioid Epidemic and Social Media with Dr. Anna Lembke*, Adjusted Reality podcast,  
<https://www.buzzsprout.com/1220486/9097921>
107. Sep 2021 *Dr. Anna Lembke / Dopamine, Addiction, Pleasure and Pain, Brokenness & The Importance of Truth*, Freedom Pact  
<https://www.youtube.com/watch?v=dbxalFNVsD0>
108. Sep 2021 *How We Became A Dopamine Nation with Anna Lembke, M.D.*, Chef AJ Live <https://www.youtube.com/watch?v=VLImiOxEQKU>
109. Sep 2021 *Are You Addicted To Your Phone?*, Viewpoints Radio  
<https://www.youtube.com/watch?v=GIpveCU61us>
110. Sep 2021 *Dr. Anna Lembke, Medical Director of Addiction Medicine at Stanford*

*University on "Dopamine Nation," Neuroscience Meets Social and Emotional Learning Podcast* <https://www.youtube.com/watch?v=5Pu82wZRZwo>

111. Sep 2021 *How our smartphones are turning us into dopamine junkies*, Radio New Zealand <https://www.rnz.co.nz/national/programmes/sunday/audio/2018812004/how-our-smartphones-are-turning-us-into-dopamine-junkies>
112. Sep 2021 *Dr. Anna Lembke – Dopamine Nation; Why We're Addicted*, ManTalks <https://www.youtube.com/watch?v=9IPrXhE-FUE>
113. Sep 2021 *Ep. 32: Dopamine Nation by Dr. Anna Lembke*, Billboard Happiness <https://podcasts.apple.com/no/podcast/ep-32-dopamine-nation-by-dr-anna-lembke/id1448644391?i=1000534719995>
114. Sep 2021 *Regulating the dopamine hit from gaming*, Hack <https://www.abc.net.au/triplej/programs/hack/hack/13518258>
115. Sep 2021 *KRTS Radio, Dr. Anna Lembke: Regulating dopamine production*, <https://soundcloud.com/550ktrs/dr-anna-lembke-regulating-dopamine-production>
116. Sep 2021 *Dr. Anna Lembke on The Zeitgeist, A Mighty Blaze* <https://www.youtube.com/watch?v=L4VBpCQ2XtI>
117. Sep 2021 *KPIX 5 CBS UPDATE: DEA Issues Safety Alert As San Francisco Fentanyl Seizures Soar* <https://sanfrancisco.cbslocal.com/2021/09/28/dea-drug-enforcement-administration-san-francisco-fentanyl-seizures/>
118. Sep 2021 *Experts Say TV Binge-Watching Feels Like A Drug, Reset with Sasha-Ann Simmons* <https://www.wbez.org/stories/experts-say-tv-binge-watching-feels-like-a-drug/24fefcf7-925b-4e92-8b51-5b4c5c0abbc0>
119. Oct 2021 *Anna Lembke - Dopamine Nation, The Hidden Why* <https://soundcloud.com/leigh-martinuzzi/1007-anna-lembke-dopamine-nation>
120. Oct 2021 *Dopamine Addiction featuring Dr. Anna Lembke*, Rehab Road Trips [https://www.youtube.com/watch?v=j0Qzbf14q\\_k](https://www.youtube.com/watch?v=j0Qzbf14q_k)
121. Oct 2021 *BNC News The Dark Side of Social Media* <https://www.facebook.com/BNCNews/videos/270205431643009/>
122. Oct 2021 *Anna Lembke, Food Junkies Podcast* <https://podcasts.apple.com/ca/podcast/food-junkies-podcast/id1547705773>
123. Oct 2021 *Podcast #745: Do You Need to Take a Dopamine Fast?*, Art of Manliness Podcast <https://www.artofmanliness.com/health-fitness/health/do-you-need-to-take-a-dopamine-fast/>

124. Oct 2021 1-hour interview with Tucker Carlson, featured on Fox Nation *Tucker Carlson Today*

125. Oct 2021 *The World Tonight* with Kelly Wright and Nayyera Haq

126. Week of Oct 11, 2021

- a. CNN New Day Atlanta, Georgia
- b. Russel Brand Under the Skin
- c. Metro.co.uk's mental health podcast, Mentally Yours
- d. Danny Zederman Armchair Nutritionist, WMVP-AM in Chicago ESPN
- e. Nervous Habits Podcast
- f. Cool Science Radio
- g. Impact Theory Podcast

127. Week of Oct 18, 2021

- a. Sirius XM Doctor Radio
- b. Melissa Monte Mindlove podcast
- c. The Rational Reminder podcast
- d. Modern Wisdom podcast
- e. Positive Sobriety podcast
- f. Wise Traditions podcast
- g. How Humans Work podcast

128. Week of Oct 25, 2021

- a. The Ben Shapiro Show
- b. Status Check with Mike Spivey
- c. Rehab Confidential
- d. Michael Gervais Finding Mastery podcast
- e. I Am Driven podcast
- f. Mark Bell's Power Project
- g. The Bill Martinez Show
- h. Superhumanize Podcast with Ariane Sommer
- i. Interview with Tom Swarbrick on UK radio station LBC <https://www.lbc.co.uk/>
- j. Impact Factor Podcast
- k. Brainwash Festival in Amsterdam
- l. Brave New World Podcast

129. Week of Nov 1, 2021

- a. Unsiloed podcast
- b. Austin McClinton podcast
- c. Mindful in May Podcast
- d. Freedom Matters Podcast
- e. Highway to Health on Sirium XM radio
- f. Yvette Le Blowitz for the Spait Girl Podcast (Australia)

- g. ABC Radio National's All in the Mind program (Australia)
- h. John Byren Dig Life Deep Podcast
- i. Phoenix arts, science, and cultural salon with Thomas Toulon

130. Week of Nov 8, 2021

- a. Welcome Home Podcast
- b. AT Banter Podcast
- c. Dr. Trish Leigh Podcast
- d. Trey Elling Books on Pod
- e. Sober Curious Podcast
- f. Endogenius Ahmed Nayel Podcast

131. Week of Nov 15, 2021

- a. Lauri Marbas Podcast
- b. San Francisco KCBS In Depth Interview
- c. Clint Malley Podcast
- d. CNN Christine Koh interview

132. Week of Nov 22, 2021

- a. Dr. Chatterjee Podcast (UK)
- b. University of Edinburgh Gregor Thomson podcast
- c. Allison Heiliczzer Webinar in Hong Kong
- d. Sober Powered Podcast with Gillian Tietz

133. Week of Nov 29<sup>th</sup>, 2021

- a. Blumatterproject Podcast
- b. Wise Traditions Podcast
- c. Next Big Idea Podcast with Rufus Griscom
- d. Soberful Podcast
- e. Parks and Recreation, Spokane, WA
- f. Tom Foxley Podcast
- g. The Parent Venture Webinar with Charlene Margot
- h. Derek Burnett from Bottom Line
- i. Mark Pearson and Tracy Wood Podcast
- j. Empowered Relationship Podcast with Dr. Jessica Higgins
- k. Resilient Recovery Podcast

134. Week of Dec 6<sup>th</sup>, 2021

- a. Body and Soul Healthy Podcast (Australia)
- b. Brian Mann NPR
- c. Jay Martin Cambridgehouse Podcast
- d. Talking to Teens Podcast
- e. Tully Podcast

135. Week of Dec 13<sup>th</sup>, 2021

- a. Best of Belfast Podcast (UK)

- b. Ukrainian popular science media Kunsht (<https://kunsht.com.ua/>)
  - c. The Breakfast Show Voice of Islam Radio Station
  - d. Dan Pierce Book Club
  - e. Psychologists off the Clock with Diana Hill
136. Week of Dec 20<sup>th</sup>, 2021
- a. Science Studio
  - b. Shin Suzuki, Reporter, BBC News Brasil;  
<https://g1.globo.com/saude/sexualidade/noticia/2021/12/28/como-pornografia-afeta-o-cerebro-e-habitos-sexuais-de-jovens-como-a-cantora-billie-eilish.ghml>
137. Week of Dec 27<sup>th</sup>, 2021
- a. Win Today with Christopher Cook Podcast
  - b. KCBS All News Radio with Mary Hughes
138. Week of Jan 3<sup>rd</sup>, 2022
- a. Roy Ben The Genuinely Interested Podcast
  - b. IMS Interview with Nervo (UK)
  - c. GovCon Different Podcast
139. Week of Jan 10<sup>th</sup>, 2022
- a. Healthier Together Podcast
  - b. The Melanie Avalon Biohacking Podcast
  - c. Louie B. Brainfood from the Heartland radio
140. Week of Jan 17<sup>th</sup>, 2022
- a. The Garden in London (UK)
  - b. Edukitchen Podcast (Rotterdam)
  - c. Drew and Liv Podcast
  - d. Preconceived Podcast with Zale Mednick
  - e. Kelly Brown Heart Media
  - f. Nimah Gobir Mindshift Podcat for NPR
  - g. Lindsay Crouse Opinion Editor NYTs
141. Week of Jan 24<sup>th</sup>, 2022
- a. Interview with Giuliano Il Venerdi (La Repubblica) - launch in Italy
  - b. Gary Collins Podcast
  - c. Metaphysical Milkshake Podcast with Rainn Wilson and Reza Aslan (Kast Media)
142. Week of Jan 31<sup>st</sup>, 2022
- a. Peter Bregman Podcast
  - b. Storybox Australia Podcast
  - c. Think Unbroken Podcast
  - d. Bradford Pope McArthur Is American Declining interview for docuseries

- e. Infotrack Radio Tour
143. Week of Feb 7<sup>th</sup>, 2022
- a. Jitender Kumar, Central European Institute of Technology, BRNO, Czech Republic
  - b. Keep Talking Podcast
  - c. A Writer Helping Writers Thrive Podcast
144. Week of Feb 14<sup>th</sup>, 2022
- a. Interview with Daniela Gassmann, editor of *Süddeutsche Zeitung Magazin*, the weekly supplement of *Süddeutsche Zeitung*, Germany's biggest daily newspaper.
  - b. Pathways Radio with Paul O'Brien
145. Week of Feb 21<sup>st</sup>, 2022
- a. Interview with Andreas Bättig from Switzerland's *Tagesanzeiger, Bernerzeitung*
  - b. Simple Families Podcast
  - c. Muscle for Life Podcast
  - d. ACE Women's Network Keynote Speaker in Georgia
  - e. Tech Addiction Investor Roundtable (London)
  - f. The Weekend University (London)
146. Week of Feb 28<sup>th</sup>, 2022
- a. Watching American, NPR Affiliate in North Carolina
  - b. THINK, KERA FM Live Radio
  - c. Open Minds Institute UCLA
  - d. Rita McGrath - Friday Fireside Chat
147. Week of Mar 7<sup>th</sup>, 2022
- a. Not Perfect Podcast - 60 mins with Poppy (Georgie Rutherford) in the UK
  - b. Anthony Sarandrea Podcast
  - c. The Super Human Life Podcast
  - d. NPR LifeKit
148. Week of Mar 14<sup>th</sup>, 2022
- a. Joe de Sena Spartan Podcast
  - b. Mario Nanos Family Forum
  - c. FUT Ballerz Podcast
  - d. Jeff Christian Podcast
149. Week of Mar 21<sup>st</sup>, 2022
- a. Clearhead Webinar New Zealand
  - b. Armchair Expert Podcast with Dax Shepard
150. Week of Mar 28<sup>th</sup>, 2022



- a. Comes a Time Podcast
  - b. Hopestream Podcast
  - c. Habits and Hustle with Jennifer Cohen Podcast
151. Week of Apr 4<sup>th</sup>, 2022
- a. Mahon McCann Podcast
  - b. John and Nick Flourishing Philosophy Podcast
  - c. The Crossover Podcast with Dr. Rick Komotar
  - d. John Slye Podcast from Grace Church, Atlanta, Georgia
  - e. Wisdom 2.0, San Jose, CA
152. Week of Apr 11<sup>th</sup>, 2022
- a. B.Rad Podcast
  - b. Aaron Kaplan podcast
  - c. Gill Tietz Podcast
153. Week of Apr 18<sup>th</sup>, 2022
- a. Thrive Global Podcast
  - b. SMART Recovery Podcast
154. November 2022 Appeared in the Netflix documentary, *Take Your Pills: Xanax*.
155. Nov 2022 CNN with Michael Smerconish, discussing *Dopamine Nation: Finding Balance in the Age of Indulgence* and smartphone addiction
156. Jun 2023 NPR's Hidden Brain with Shankar Vedantam discussing *Dopamine Nation: Finding Balance in the Age of Indulgence*
157. Jun 2023 *Spark* on the Canadian Broadcasting Corporation, discussing *Dopamine Nation: Finding Balance in the Age of Indulgence* and smartphone addiction
158. Jun 2023 South Korea's *Money Time*, discussing *Dopamine Nation: Finding Balance in the Age of Indulgence*

*Lembke Report*

*Confidential — Subject to Protective Order*

# Anna Lembke, M.D. Report

## EXHIBIT B

### List of Materials Considered

**DR. ANNA LEMBKE MATERIALS CONSIDERED**

1. 21 C.F.R. §1300.01 - Drug Enforcement Administration, Department of Justice. Definitions.
2. 22 Tex. Admin. Code § 170.3 (Amended 2020)
3. 84(R) SB 1462 - TX Opioid Agonist Legislation
4. A Community of Recovery, Dayton, Ohio's Compassionate, Collective Approach to the Opioid Crisis by Erin Welch January 2019. [https://americanprogress.org/wp-content/uploads/2019/01/DaytonOpioid-report.pdf?\\_ga=2.96221020.1179087810.1655914639-1647710228.1655914637](https://americanprogress.org/wp-content/uploads/2019/01/DaytonOpioid-report.pdf?_ga=2.96221020.1179087810.1655914639-1647710228.1655914637)
5. AARP Prescription Discounts provided by OptumRx. <https://aarp-pharmacy.com/assets/images/faqPage/faq-infographic.pdf>
6. Abbasi AB, *et al.* Opioid prescribing patterns before fatal opioid overdose. *Am J Prev Med.* 2020;58(2):P250-253.
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14. Agency for Healthcare Research and Quality, Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings (2016)
15. Agniel, D., *et al.* Association of Postsurgical Opioid Refills for Patients With Risk of Opioid Misuse and Chronic Opioid Use Among Family Members. *JAMA Network Open.* 2022;5(7):e2221316. doi:10.1001/jamanetworkopen.2022.21316

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20. Ajay Manhapra MD, Albert J. Arias MD & Jane C. Ballantyne MD (2018) The conundrum of opioid tapering in long-term opioid therapy for chronic pain: A commentary, *Substance Abuse*, 39:2, 152-161
21. Alameda ED Visit. Opioid-related overdose. CA Opioid Dashboard
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2893. ALB-MDLCT9-00091915  
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2903. ALB-MDLCT9-00208037  
2904. ALB-MDLCT9-00210097  
2905. ALB-MDLCT9-00135435

2906. ALB-MDLCT9-00014010  
2907. ALB-MDLCT9-00014011  
2908. ALB-MDLCT9-00188951  
2909. ALB-MDLCT9-00207824  
2910. ALB-MDLCT9-00207825  
2911. ALB-MDLCT9-00041067  
2912. PUBLIX-MDLT8-00074321

*Lembke Report*

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# Anna Lembke, M.D. Report

## EXHIBIT C

### Statement of Compensation Rate

*Lembke Report*

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Anna Lembke, M.D.  
Stanford University School of Medicine  
Department of Psychiatry and Behavioral Sciences

**Expert Witness Fee Schedule:** *Case No. 1:18-op-45817-DAP*

Work	Details	Fee
Preliminary Work	Telephone conferences, record review, report writing, and travel	\$500 per hour
Court Work	Court appearances and depositions	\$800 per hour
Expenses	Travel and other reasonable out-of-pocket expenses	Reimbursement

Ex. C - 1

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# Anna Lembke, M.D. Report

## EXHIBIT D

Prior Testimony

*Lembke Report*

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Anna Lembke, M.D.  
Stanford University School of Medicine  
Department of Psychiatry and Behavioral Sciences

**Prior Testimony**

- *People v. Philip Morris Ingram*, (Cal. Super. Ct., Docket 62-144622)
- *National Prescription Opiate Litigation*, MDL No. 2804 (N.D. Ohio, Case 1:17-md-2804)
- *In Re Opioid Litigation*, (Suffolk County, New York Supreme Court, Index No. 400000/2017), relating to Case Nos. County of Suffolk, 400001/2017; County of Nassau, 400008/2017; and New York State, 400016/2018
- *Cabell County Commission and City of Huntington, West Virginia, (The Cabell Huntington Community) v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation*, No. 1:17-op-45053-DAP and No. 1:17-op-45054
- *People of the State of California v. Purdue Pharma, L.P., et al.*, No. 30-2014-00725287-CU-BT-CXC
- *Miner v. Olsen, et al.* (arbitration)
- *The County of Lake, Ohio v. CVS Health Corporation., et al.*, No. 18-op-45032 and 18-op-45079
- *County of Dallas, Texas vs. Johnson & Johnson, et al.*, No. 3:18-cv-00426-M and Cause No. DC-18-00290
- *City and County of San Francisco et al. v. Purdue Pharma, LP et al.* No. 3:18-cv-07591-CRB
- *The Montgomery County Board of County Commissioners, et al. v Cardinal Health Inc. et al., Case No 1:18-op-46326-DAP*

Ex. D - 1